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SULPHANILAMIDE AND SULPHAPYRIDINE IN EXPERIMENTAL CEREBRAL WOUNDS

BY

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THE local use of sulphanilamide and sulphapyridine in wounds is proving valuable both by preventing infection and in controlling established infection. These drugs may be expected to have the same bacteriolytic and bacteriostatic effects in cerebral wounds as in wounds of other tissues, for the reaction of the brain to wounding and infection is basically similar. The reaction of other tissues to these drugs has not prevented their use locally in wounds. Healing has been shown to be delayed slightly but not significantly. Acute inflammatory reaction in response to the presence of sulphanilamide or sulphapyridine has been transitory in most tissues even though large amounts of drug have been applied. In cerebral wounds the inevitable local reaction to any foreign material and the potential remote toxic effects on nerve cells, neuroglia, and myelin may make it undesirable to implant sulphonamides. The purpose of these experiments was to determine whether such undesirable local and remote reactions followed the introduction of large amounts of sulphanilamide or sulphapyridine into cerebral wounds, and if they were sufficiently marked to contra-indicate their use. Observations were also made on the time taken for the drugs to disappear from the wounds, the levels of each drug reached in the blood, and the reaction of the tissue to these two drugs.

Experimental procedure

Defects were made in the cortex and white matter of one or other cerebral hemisphere in a series of thirty cats. Twenty-four experiments were satisfactory for our purpose. Following the incision of the pia mater, cerebral tissue was crudely excised by blunt dissection. Careful and repeated wiping out of the

wound with gauze produced a cavity large enough to contain approximately barely 500 mgm. of the drug. When it was not large enough to hold 500 mgm. of drug it was spilled over into the subdural space, covering the leptomeninges near the excision. The defects measured 1–1½ cm. in diameter. In some of the animals openings were made into the ventricles while in others the excisions were superficial to the ventricle. The dura was not sutured but the temporal muscle, when replaced, closed the dural opening and small bone defect. The operations were carried out under either intravenous or intraperitoneal nembutal anæsthesia.

Certain technical details should be mentioned, for they may bear on our conclusions. The heads were shaved, scrubbed with soap and water, and painted with metaphen in alcohol and acetone. Sterile towels were used as drapes. The surgeon scrubbed for ten minutes, soaked his hands for about a minute in 1 in 1,000 mercuric potassium iodide, but wore no gloves, cap, or mask. The chemically pure, finely-powdered sulphanilamide and sulphapyridine had each been put up in sealed glass ampoules containing 500 mgm. The outside of the ampoules was sterilized by boiling for ten minutes. Sometimes, when the ampoules were broken, small pieces of glass fell into the crystals of drug and, unrecognized, were put into the wound with the drug.

It was often observed that hæmorrhage ceased when a wound cavity was heavily coated with sulphapyridine and light pressure applied. When sulphanilamide was used the same effect was not obtained. This may be due to the greater solubility of sulphanilamide. Again, sulphapyridine forced into venous channels of the cat's skull and held there frequently stopped bleeding effectively though less promptly than Horsley's bone-wax. We accordingly concluded that sulphapyridine in stopping bleeding probably acted only as a mechanical agent.

The general health of these animals was excellent once they had recovered from the immediate effects of the anæsthetic and operation. In no instance was any disability attributed to the local use of either sulphapyridine or sulphanilamide.

Results

Time required for relatively large amounts of drug to disappear from cerebral wounds

SULPHANILAMIDE

Brain defects were made superficial to the ventricle in eight cats and into the lateral ventricle in three cats. For reasons to be discussed later these eleven experiments will be considered as one group. The durations of the experiments were as follows : less than 24 hours, 2 days, 6, 18, 18, 27, 36, 46, 90, 93, and 95 days. One animal died during the first day from intracerebral and intraventricular hæmorrhage. Crystals of drug mixed with blood filled the brain defect. A second animal, killed after two days, had never recovered consciousness as a result of hæmorrhage into the drug-filled defect and surrounding brain. Masses of crystals were present. In the third cat a

spongy mass of crystals mixed with red blood cells filled the brain defect on the sixth day. Two animals were killed on the eighteenth day after operation, and in these no drug could be seen in the brain wounds with the unaided eye. In both animals a small amount of yellow pigmented sludge was present deep to the dural scar. Microscopical studies showed a few spaces at the site of cerebral injury of one of these eighteen-day cats, indicating that crystals of sulphanilamide in free or acetylated form had been dissolved out. The reason for this opinion will be discussed in a later section.

No drug was found macroscopically in the brains of any of the six animals

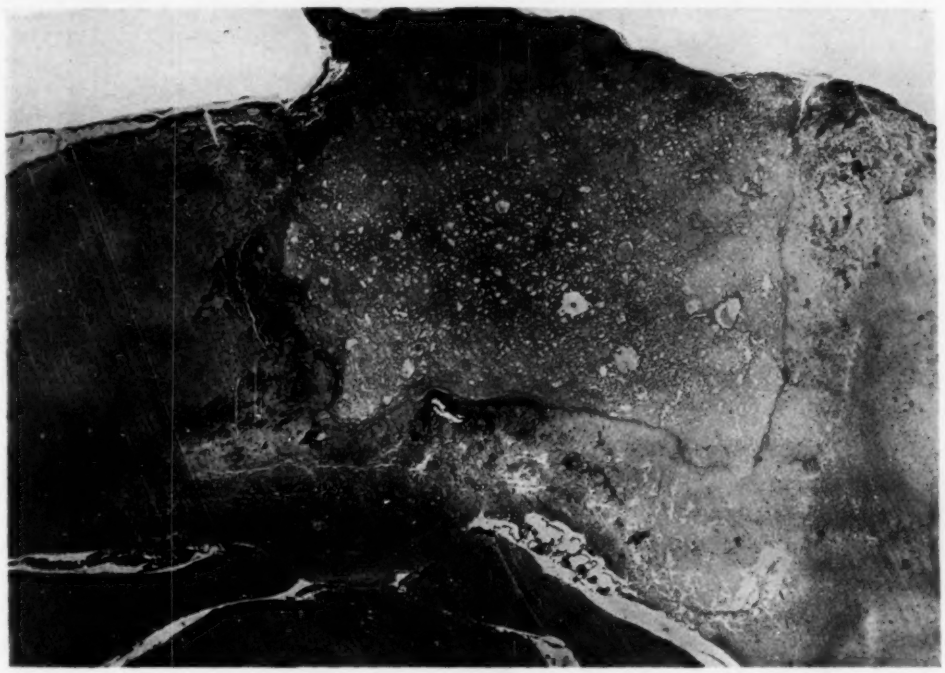

Fig. 1.—The cerebral defect was still filled with crystals of sulphanilamide 6 days following operation.

killed 27, 36, 46, 90, 93, and 95 days after operation, but microscopically, spaces which probably contained sulphanilamide crystals were found in the scar of the 27-day animal. This was the longest period after operation that any microscopical evidence was found suggesting the presence of sulphanilamide.

SULPHAPYRIDINE

In eight animals sulphapyridine was placed in wounds superficial to the ventricle, while in five animals the ventricle was opened. These thirteen animals will also be considered as a single group. The duration of the various experiments was 2, 8, 14, 16, 30, 44, 44, 51, 58, 61, 63, 88, and 108 days. Large quantities of crystals were seen in the cerebral wounds of 2, 8, 14, 16, and 30-day experiments. Beyond the 30-day period the drug was found in but one cerebral scar and that was as an encysted island of crystals measuring $2 \times 3 \times 8$ mm. in an animal killed after 51 days. It is noteworthy that neither of the 44-day

experimental wounds contained any crystals. When the drug was not recognized with the unaided eye it was not found microscopically.

In considering the time taken for sulphanilamide or sulphapyridine to disappear from brain wounds, several reasons impelled us to group all the experi-

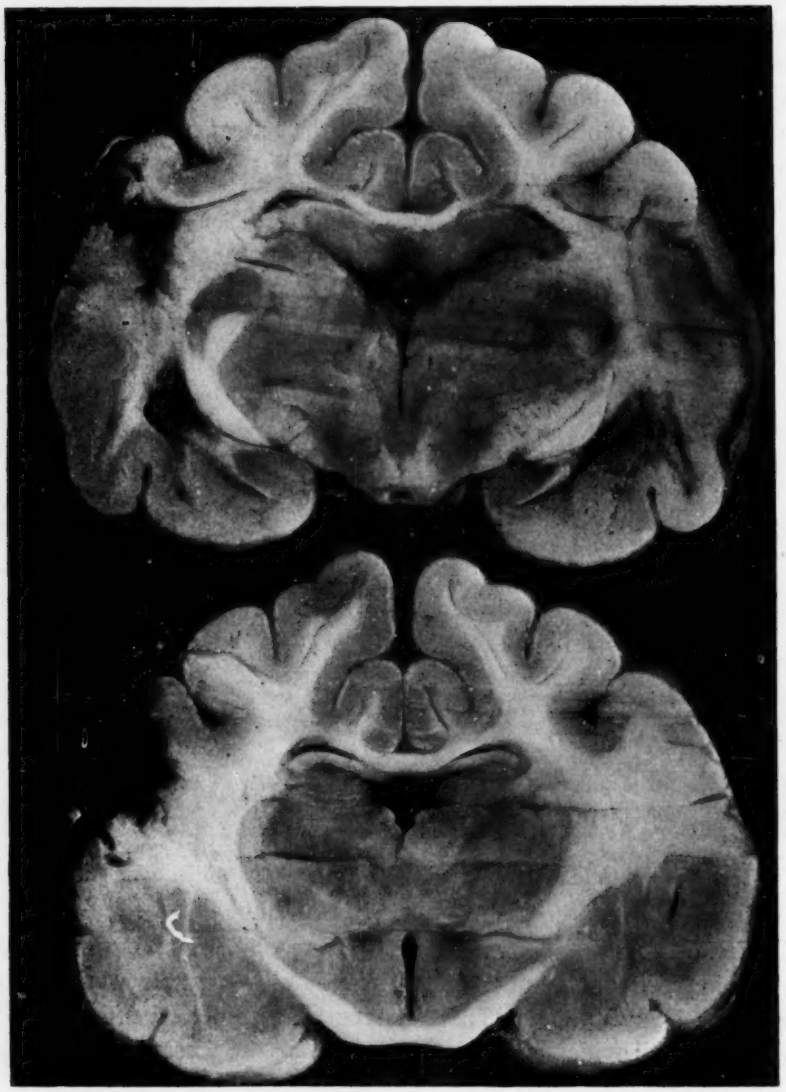

Fig. 2.—18 days following the operation and implantation of sulphanilamide no gross drug was seen. A cystic pigmented scar was present with a thin layer of amorphous pigment immediately deep to the dural scar. Microscopically spaces were found which probably contained crystals.

ments together irrespective of whether or not there was an opening into the ventricle. In some instances the ventricle was widely opened, while in other operations ventricular fluid seeping into the wound was the only evidence of an opening. The length of time during which ventricular fluid washed away the drug, and in what quantity, would in part depend on the size of the opening

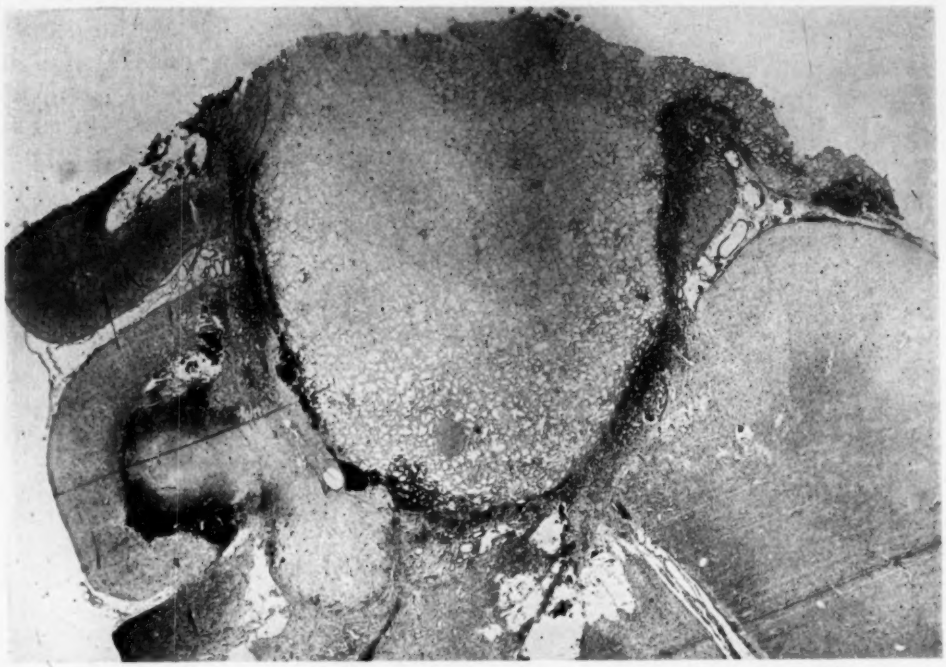

Fig. 3.—14 days after operation sulphapyridine was found completely filling the cerebral defect and overflowing into the sub-dural space. The encapsulation of the drug is well shown.

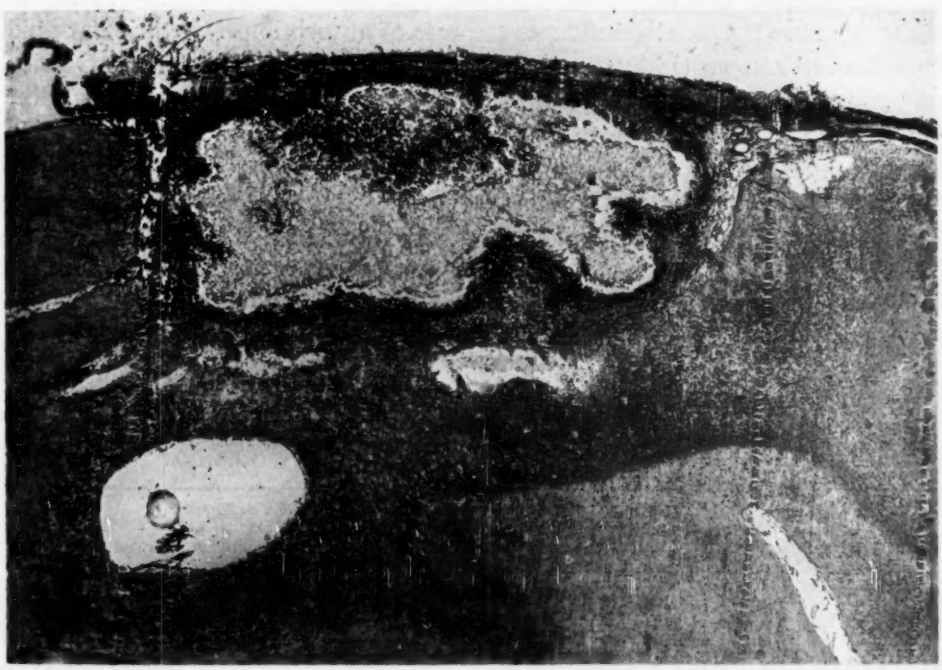

Fig. 4.—30 days following implantation of sulphapyridine, a large amount of crystalline drug was still present. The encapsulation was heavier, and finger-like collections of phagocytes projected from the periphery into the crystalline mass of drug.

Fig. 5.—108 days after implanting sulphapyridine no drug was present. The excision extended down to the ependymal lining of the lateral ventricle. The large defect was filled with a loose spongy neuroglia connective tissue matrix. The lateral ventricle on the side of the wound was dilated.

into the ventricle and how long the opening remained patent. The solubility of the drug used must also influence the rate of absorption by ventricular fluid Russell and Falconer (1940) quoted a personal communication from J. O'Brien indicating that 1,250 mgm. of sulphanilamide or 85 mgm. of sulphapyridine will dissolve in 100 c.c. of normal C.S.F. incubated at 35° C. for 14 hours. In our experiments the drug became encapsulated after some days, regardless of an opening into the ventricle, thus minimizing the passage of the drug into ventricular fluid. For these reasons, it appears unnecessary to divide the experiments into two groups : namely, those with open and those with closed ventricles.

Absorption of Sulphapyridine and Sulphanilamide

SULPHAPYRIDINE

Blood levels were estimated daily in a group of animals during the 3-day period following operation. The following results were obtained :

24 HOURS mgm. per cent.		2 DAYS mgm. per cent.		3 DAYS mgm. per cent.	
Free	*Total*	*Free*	*Total*	*Free*	*Total*
0·1	1·1	0·7	1·1	0·71	not done
0·74	not done	1·2	1·4	0·5	,,
1·2	1·2	1·3	1·6	—	,,
1·3	1·4	1·0	1·1	0·65	,,
1·15	1·5	0·59	not done	0·9	,,
		1·78	2·0		

These levels were so low that only occasional further blood specimens were taken during the periods of survival in addition to an immediate ante-mortem one. Between the 4th and 30th post-operative days 15 blood estimations ranged from " very low " to 0·67 mgm. per cent. free sulphapyridine. In two instances total sulphapyridine was estimated as well as free ; 11 days after operation the figures per cent. free and total respectively were 0·3 and 0·78 mgm., and at 30 days 0·25 and 0·3 mgm. Between 11 and 30 days after operation, six specimens of urine were tested for the presence of the drug. The following table indicates the amounts obtained.

DAYS AFTER OPERATION	BLOOD SULPHAPYRIDINE mgm. per cent.		URINE SULPHAPYRIDINE mgm. per cent.	
	Free	*Total*	*Free*	*Total*
11	0·4	not estimated	19	not estimated
11	0·2	" "	14·3	" "
15	—	—	14·5	" "
18	v. low	not estimated	10·0	" "
22	0·27	" "	8·35	" "
30	0·25	0·3	0·5	2·7

No drug was present in the urine of two cats on the 88th and 108th days after operation. Of five animals killed 41, 44, 51, 58, and 63 days after operation, no drug was found in the blood at the time of death. Cerebrospinal fluid was tested, prior to sacrifice, from another 44-day animal as well as from the 44, 58, and 63-day animals and found to contain no drug. It was noteworthy that there was an island of drug $2 \times 3 \times 8$ mm. in the cerebral scar of the 51-day animal. The urine of this animal was not tested at the time of death.

SULPHANILAMIDE

In two cats the blood levels of free and total substances after 24 hours were 0·6–0·67 mgm. per cent. and 0·55–0·61 mgm. per cent. respectively. In another animal a reading of 0·81–1·0 mgm. per cent. was obtained after 6 days. Seven further specimens from the series of animals were obtained ranging from 11 to 36 days after operation. Drug was found, 0·2–0·22 mgm. per cent. in only one blood 22 days after operation. It will be recalled that no gross drug was found in the brain of any animal killed after the 6th day, although microscopical examination indicated spaces which probably contained crystals of sulphanilamide in one of two 18-day animals and in the 27-day animal.

Macroscopical findings

The brains were fixed in situ by intracarotid injection with either Cajal's ammonium bromide or 4 per cent. formalin (10 c.c. of 40 per cent. formalin per 100 c.c. tap water). In those animals in which clotting prevented fixation by this method, the brains were removed and suspended in the fixative to harden before sectioning. The dura and temporal muscle over the brain wound was always left attached to the brain during the fixing process.

There was no macroscopical evidence, regardless of the length of post-operative survival, that sulphanilamide or sulphapyridine caused either œdema of the injured hemisphere or of the other hemisphere. This was evident in parallel coronal sections, which disclosed no asymmetry of the hemispheres. The width and sharpness of outline of the grey matter were identical on the two sides when comparable areas were measured. The corona radiata were symmetrical. No herniation of the brain took place, though the dura had been left open. The leptomeninges away from the wounds appeared to be normal. In all experiments, regardless of whether or not the ventricle had been opened, the ependyma of the lateral third and fourth ventricles was smooth and glistening. The aqueduct of Sylvius was always patent.

Examination of the brain wounds of animal which did not recover from the anæsthetic or did not regain consciousness within 24 hours of operation showed that the operative removal of cortex had lacerated grey matter and caused irregular pockets and areas of hæmorrhage of varying size in the white matter some considerable distance from the wound. The satisfactory wounds were comparable to the wounds left in human beings after debridement of serious lacerated wounds of the brain.

In experiments terminated as early as the 8th day a delicate capsule was recognized around the implanted drug. Thick capsules developed about sulphapyridine in the later stages. Around sulphanilamide the same connective tissue encapsulation occurred, but never reached similar thicknesses to those around implanted sulphapyridine. The difference in this degree of encapsulation may be explicable on the different solubilities of the two substances. In the later stages with complete disappearance of both drugs the capsule became less prominent and the region of the wound appeared as a loose-meshed spongy yellowish tissue, usually cystic but sometimes containing pigments. The ventricle adjacent to the wound was found enlarged, especially when the drug had disappeared and the inflammatory reaction had subsided. Bone marrow, kidneys, ureters, and the bladder showed no evidence of having been affected by the drugs in any of the experimental animals.

Microscopical findings

A composite description of the microscopical findings will be given rather than a detailed report of the findings in each experiment. The earliest reactions about either drug was an outpouring of polymorphonuclear leucocytes, which formed a heavy though uneven mantle around the crystals and even penetrated for a short distance into the mass. Phagocytic cells made their appearance at an early stage and formed a zone outside the polymorphonuclear cells. In this zone lymphocytes appeared, fibroblasts differentiated, and reticulum was laid down.

As the polymorphonuclear leucocytic reaction became less intense the cells degenerated and fragmented nuclear chromatin was scattered at the border zone between the drug and the phagocytes. Phagocytes increased in number and insinuated themselves between the crystals at the margins of the

drug. At a later stage multinucleated phagocytes (giant cells) became numerous in this zone about the crystals. The way in which the phagocytes next to the crystals elongated and oriented themselves at right angles to the developing capsule as they invaded the crystals was striking. At later periods plasma cells were found mixed with the lymphocytes, and in the brain tissue adjacent to the outer layer of this reaction phagocytes were present.

As the drug disappeared the inflammatory reaction subsided and giant cells became less numerous. When the sulphanilamide crystals disappeared a loose meshwork of astrocytes and connective tissue surrounded small cysts containing some phagocytes. In this meshwork and around the blood vessels there were a few lymphocytes and plasma cells. At this stage the giant cells had disappeared.

The scars in the longest experiments contained much less connective tissue than had been anticipated, in view of the intensity of the inflammatory reaction at certain periods and its duration. The well-formed connective tissue capsule seen at the intermediate periods when the drug had not been completely absorbed entirely disappeared. The amount of collagenous connective tissue was greater in the wounds filled with sulphapyridine.

In a microscopical study it was found that the microglia underwent transition to the phagocytic form near the drug and altered for a short distance from the wounds in the white matter to rod forms and phagocytes. Astrocytes in the immediate vicinity of the wound underwent the classical changes, showing first hypertrophy and then increase of neuroglia fibres. Away from the wound the astrocytes were normal. No reaction of the astrocytes was observed in the normal hemisphere. Oligodendroglia was more readily stained than usual in the hemisphere on the side of the operation. No other definite alteration in it was made out. Normal cells were present quite close to the area of wounding. Neurofibril and nerve cell stains, as also stains for myelin, disclosed no abnormality away from the wound or in the opposite hemisphere.

While the macroscopical examination had shown no changes in the leptomeninges away from the traumatized area polymorphonuclear leucocytes and phagocytes were found microscopically in the subarachnoid space in the shorter experiments and lymphocytes and phagocytes in the later ones. This reaction was confined to the subarachnoid space in the neighbourhood of the wound. No other constant abnormality was made out.

It was interesting that in both experiments in which a wide opening had been made into the ventricle the drug nevertheless was found to be encapsulated. When a transventricular wound was made encapsulation still took place with partial blocking of the ventricle. As absorption and healing occurred transventricular septa remained to distort the ventricular outline.

Qualitatively the reaction to sulphanilamide and sulphapyridine was the same. Quantitatively there was a difference. More polymorphonuclear leucocytes surrounded sulphanilamide than sulphapyridine crystals in the early stages after implantation. With sulphapyridine, which took approximately twice as long to absorb as sulphanilamide, the inflammatory reaction was prolonged and the connective tissue encapsulation was thicker. However, in the

longest experiments the scarring was no more intense in the wounds treated with sulphapyridine than it was in those filled with sulphanilamide. For example, in wounds of 90 and 108 days much of the mesodermal reaction had disappeared and it was impossible to determine by study of sections which drug had been implanted.

No microscopical abnormalities due to the drugs were found in the bone marrow or kidneys of any of the experimental animals.

Comment

The cerebral defect produced at operation was large in proportion to the size of the cat's brain, and because of the operative technique used the lesions simulated in many ways a deep wound in the human brain following an incomplete debridement. In this series of animals 500 mgm. of either sulphanilamide or sulphapyridine disappeared completely from wounds in the brain. It is estimated that a comparable quantity of these drugs applied to an injury of the brain of man would amount to from 25 to 50 gm. This comparison may serve to demonstrate the severity of the test to which local application of sulphonamides was put. Our experiments indicated that the intensity and duration of the inflammatory reaction depended upon the quantity of drug used, its solubility, and the length of time it remained in the wound. Though large amounts of drug were implanted, if the animals survived as long again, or even longer, than had been shown requisite for these drugs to disappear, there was but little ultimate connective tissue scarring. At most a loose-meshed mixture of neuroglial cells and a small amount of connective tissue surrounded small cysts containing phagocytes. This type of scar occurred with both sulphapyridine and sulphanilamide. Some of the late scars were as satisfactory as those following experimental wounds carried out with extreme care and without implantation of any absorbable foreign bodies.

Under the circumstances of these experiments using about 500 mgm. of drug, sulphanilamide disappeared completely in from 18 to 36 days and sulphapyridine from 44 to 58 days. Russell and Falconer (1940) found that a pellet of 1 mgm. of sulphapyridine injected hypodermically into the cortex of a rabbit's brain disappeared within four days and 1 mgm. of sulphonamide within twenty-four hours. They also observed a foreign body reaction characterized by the presence of phagocytic foam cells and multinucleated giant cells. Hurteau (1941) inserted about 100 mgm. of drug into wounds in the brains of cats and then used the chemical method of Maher and Camp (1938) to test for the presence of sulphonamide in the cerebral substance. Sulphapyridine was not detected after 34 days, sulphathiazol after 17 days, and sulphanilamide after 11 days. The relation between the quantity of drug inserted and time required for the drug to be absorbed is apparent if the results of our experiments are contrasted with those obtained by Russell and Falconer and by Hurteau.

Final conclusions have not yet been reached as to how valuable sulphanilamide and sulphapyridine are as bacteriostatic and bacteriolytic agents when applied locally. Experimental and clinical data are accumulating which

suggest that their *in vitro* action is duplicated in wounds, high concentrations of sulphanilamide having significant bacteriostatic and bacteriolytic effects on a variety of organisms. In our experiments sulphanilamide was absorbed much more quickly from wounds of the brain than sulphapyridine, and the resultant inflammatory and foreign body giant cell reactions were therefore so much shorter that it is probably the drug of choice for local application in wounds of the brain. It can be more generously applied than sulphapyridine or sulphathiazol.

Consideration of the results of these experiments, in relation to the problems of treatment of injuries to the brain of man, indicates that the local foreign body reaction does not contra-indicate the application of sulphanilamide or sulphapyridine. Regardless of which sulphonamide is applied to a cerebral wound locally, excessive quantities of drug should not be used, and in all probability a thin layer coating the walls of the wound should be considered sufficient if sulphapyridine is used.

Local implantation does not provide a depot from which absorption will take place and give adequate blood levels. The low levels of both sulphanilamide and sulphapyridine reached in the blood, a maximum of 0·67 mgm. per cent. and 1·78 mgm. per cent. respectively of the free drugs, are not accepted as being of therapeutic value. No estimations were possible of the drug levels attained by either sulphanilamide or sulphapyridine in the region of these cerebral wounds.

No attempt has been made in this series of experiments to assess the therapeutic value of using sulphanilamide or sulphapyridine, but it is of interest that there was no instance of deep infection or meningitis among the thirty cats operated on. The brain wounds were purposely of a lacerated type, and it is not uncommon in such a series of laboratory experiments to have an occasional infection of a cerebral wound ; it is therefore all the more remarkable that no wound was infected in this series.

One very practical point in surgical technique comes from this work. Sulphapyridine crystals may be used effectively to control bleeding from small- and medium-sized venous channels in bone by blocking the opening.

Summary

After 500 mgm. of pure sulphanilamide were placed in brain defects, crystals were found up to the 6th day but not on the 18th day post-operative. Microscopically drug was probably still present on the 27th day but not on the 36th day after operation.

It required from 44 to 58 days for an equal amount of sulphapyridine to be completely absorbed.

No impairment in the general health of the animals was attributed to the local use of sulphanilamide or sulphapyridine. No damage to liver, bone marrow, kidneys, or bladder was discovered.

The highest levels of either sulphanilamide or sulphapyridine found in the

blood, resulting from absorption of drug implanted in the cerebral wounds, were never sufficient to be of therapeutic value.

Both drugs act as foreign bodies as long as they persist in cerebral wounds. The tissue reaction is a local one and the drugs are eventually encapsulated. When absorption is complete the inflammatory reaction subsides. The quality of the local reaction to the two drugs is the same. Rather more polymorphonuclear leucocytes surround sulphanilamide than sulphapyridine in the early stages. Sulphapyridine takes approximately twice as long to disappear from a brain wound as does sulphanilamide, and there occurs a heavier connective tissue encapsulation.

No undesirable side effects were observed on nerve cells, neuroglia, or myelin at a distance from the drugs. The reaction remained as a local one.

In the longest experiments the cerebral scars did not seem more extensive or more active than scars following wounds studied in previous series of experiments and uncomplicated by the local use of sulphonamides.

As a result of these experiments we have not hesitated to use sulphonamides in potentially infected or infected wounds of the human brain, but we have used them circumspectly. We shall continue to use them guardedly even when their local bacteriostatic and bacteriolytic action is proven beyond doubt, for they do act also as foreign bodies.

This work was carried out on behalf of the Medical Research Council at the Research Unit of the National Hospital, Queen Square, London, W.C.1. Messrs. May and Baker, Ltd., kindly provided the drugs used throughout the investigation.

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ILLUSTRATIONS

The illustrations were chosen to demonstrate the relatively early disappearance of 500 mgm. of sulphanilamide from a wound in the brain in contrast to the later disappearance of 500 mgm. of sulphapyridine. The oldest wound, studied 108 days following operation, is shown because it is typical of the extent of the excisions carried out and the amount of the scarring present at this stage.

A CONGENITAL FORM OF AMAUROTIC FAMILY IDIOCY

BY

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(RECEIVED 11TH NOVEMBER, 1941)

SINCE the original description of Tay-Sach's disease in the eighties of the last century a group of allied nervous disorders has become recognized, the common pathological feature of which is a ubiquitous distention of the nerve cells with granules of a lipoid nature. Apart from a few anomalous forms it is customary to classify these amaurotic family idiocies according to the time of onset of the disease, infantile, late infantile, juvenile, late juvenile and adult types being described. The resemblance between the infantile type and Niemann-Pick's disease had been noted by Knox, *et alia*, in 1916, but it was not until Pick and Bielschowsky's (1927, 1928) demonstration of the closely similar cerebral pathologies of these two conditions that it became generally realized that disordered lipoid metabolism, not heredodegeneration, was responsible for the granular accumulations in the nerve cells. The consequent inclusion of the amaurotic family idiocies in the category of lipoidoses began a new chapter in the history of these much studied diseases and support for this new theory of pathogenesis has since been received from the occasional finding of the characteristic type of neuronal swelling in the predominantly mesodermal disorders of Gaucher (Lindau, 1930) and of Hunter-Hurler (Ashby, *et alia*, 1937). Nevertheless, in many, perhaps most, cases of amaurotic family idiocy lipoid storage is confined to the nervous system, and it might well seem a perversion of nomenclature to classify these apparently purely nervous diseases as "lipoidoses" were it not that in some otherwise typical examples of the infantile and juvenile forms unsuspected lipoid storage in the visceral organs has been found on microscopical search (Schob, 1930; Pick, 1932; Brouwer, 1936). The case recorded in this paper belongs to this theoretically important intermediate group which is characterized by the predominantly cerebral localization of the lipoid deposition, the reticulo-endothelial system being involved only in a minor degree. It differs, however, from Tay-Sach's disease in several respects, notably in its congenital character and in the histochemical reactions of the intracellular lipoid.

Case Report

Baby C., a full-term female infant, was born after a normal labour in Southmead Hospital, Bristol. The mother's pregnancy had been uneventful. A few days after birth it was noticed that the baby became slightly blue during her feeds and later regurgitated fluids immediately after feeding. A catheter was passed down the œsophagus, but no abnormality was found. Blood was found in the napkins for 5 days before death, which occurred at the age of 18 days and the cause of which was obscure.

Family History.—The father and mother were interviewed. They are normal physically and mentally, are not blood relatives, and have two other normal children. A brother of the father is a certified mental defective. An aunt of the father resided for many years in a Public Assistance Institution suffering from unspecified mental trouble, but is now at her home and is not regarded by her relatives as abnormal. We have been unable to verify this. Apart from these two relatives there is no history of mental illness in the family, and neither parent nor a paternal aunt who was also visited could recall any death in infancy or childhood among the numerous family connections.

Post-Mortem Examination.—The body was rather wasted and severely dehydrated. The skin showed no abnormality. The head appeared small (circumference 28 cm.), but the facies was normal. The lungs were completely aerated and showed a small subpleural hæmorrhage at one point. The larynx appeared small, the trachea being normal and showing no communication with the œsophagus. The walls of the ventricles of the heart were equally thick and a patent ductus arteriosus was present which admitted easily a probe 2 mm. in diameter. There was no coarctation of the aorta. At the lower end of the œsophagus a small ulcer was found, probably the result of the passage of a catheter during life. There was no congenital abnormality of the gut. A small amount of altered blood was present in the colon, the mucosa of which showed patchy engorgement. Both kidneys showed gross hæmorrhages into a number of individual pyramids. The ureters and urinary bladder were normal, the latter containing blood-stained urine. Spleen, lymph glands, adrenals, thyroid, thymus, pancreas, ovaries and uterus showed no naked eye abnormality. The liver was somewhat pale, but otherwise appeared normal. The calvaria had the usual extent of ossification. A considerable degree of external hydrocephalus was found, a wide fluid filled space being present between the surface of the brain and the dura. Over the superior surface of the hemispheres the leptomeninges floated in loose folds.

Microscopical Examination of the Kidneys.—Massive diffuse hæmorrhages apparently of capillary origin were present between the tubules of the affected pyramids. Many of the tubules contained red blood cells. There was no evidence of organization, leucocytes were scanty and conspicuous amounts of hæmatogenous pigment in the form of fine granules were present. Around the areas of hæmorrhage was a narrow zone of capillary dilatation with some diapedesis of red cells. Large groups of glomeruli, not obviously related to the areas of hæmorrhage, showed engorgement of the glomerular tufts, but otherwise the cortex appeared normal for a child of this age. Changes in the tubular epithelium were probably the result of post-mortem autolysis. Fat staining showed no abnormality.

Macroscopical Examination of the Nervous System

The meninges stripped easily. The brain was much smaller and lighter than that of a newly born child, its length being 6½ cm. and its weight with

cerebellum and brainstem only 87 gm. Cerebellum and brainstem weighed 5½ gm. The convolutional development was peculiar, the frontal lobes showing a relative pachygyria (Fig. 1). The Rolandic sulci were clearly formed, though neither reached the great longitudinal fissure. The precentral sulcus on the left side was present in two parts, but that of the right side was represented only by a short sulcus in the lateral aspect of the brain. Shallow indentations marked the superior and inferior frontal sulci, the superior frontal gyrus appearing unduly broad for so small a brain while at the frontal pole the cortex was smooth apart from a few irregular undulations. Operculation in the region of the third frontal gyri was well advanced and the insulæ were not unduly exposed. On the ventral aspect of the frontal lobe only the gyri recti were represented. The temporal, parietal and occipital lobes showed a more advanced degree of convolutional development, but no secondary sulci were present. The sulci were shallow and gaped widely in a manner suggestive of atrophy. The cerebellum (Fig. 1) was obviously small compared with the size of the brain as a whole, the lateral lobes in particular being poorly developed, the vermis being entirely exposed and the whole organ appearing dumb-bell shaped. The cerebellar sulci were also shallow and unduly wide and the convolutions adjoining the posterior cerebellar notch appeared completely atrophic. On palpation, the brain was much firmer than normal, but not in a uniform manner, the cortex being softer than the deeper portion of the hemispheres. This deep-seated toughness was more apparent after section of the brain, especially in the thalami and brain stem. There was evidently a gross reduction in the volume of the cortical white matter and the subcortical white matter of the frontal lobe showed a rarefaction and shrinkage of the tissue suggesting a status spongiosus (Fig. 2). The cavum of the septum pellucidum was dilated, but the lateral ventricles showed no obvious hydrocephalus. The corpus callosum was represented by a tough ribbon-like structure widening in the genu and splenium to a width of about 3 mm.

Microscopical Examination of the Nervous System

Cerebral Cortex.—Numerous representative areas were examined from the left cerebral hemisphere, standard methods for nerve cell bodies, axis cylinders, myelin, lipoid and neuroglia being employed. No abnormality was found in the pia-arachnoid. The cortex was sharply demarcated from the subjacent white matter and measured in depth from 0·8 mm. in the occipital pole to 1·3 mm. in the frontal lobe. When stained by cresyl violet or toluidine blue the grey matter was seen to be richly cellular, an abnormally large astrocytic type of nucleus predominating.

Nerve Cells were by no means obvious owing to the absence of Nissl granules. The most easily recognized were the Betz cells of the precentral gyrus which showed gross swelling and uniform staining of their cytoplasm (Fig. 5). Elsewhere, chiefly in the deeper layers of the pre-frontal, insular and hippocampal areas, nuclei of neuronal type were found in cells showing an

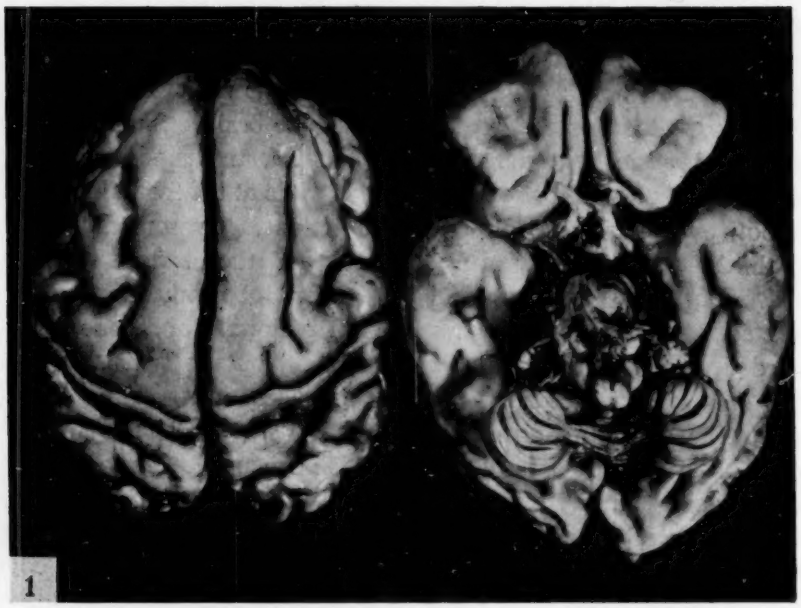
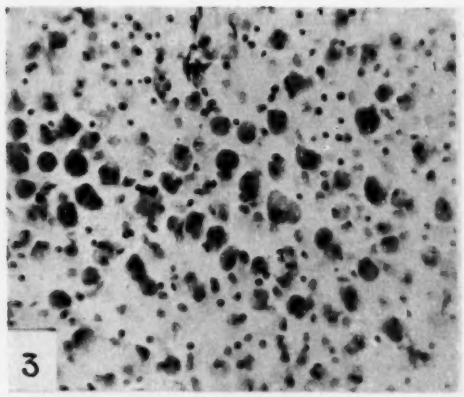


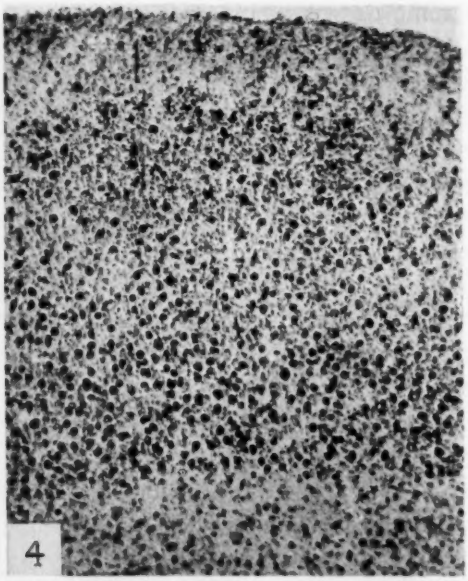
Fig. 1.—Superior and inferior surfaces of brain showing pachygyria of frontal lobes, gaping sulci, and small cerebellum. Natural size.

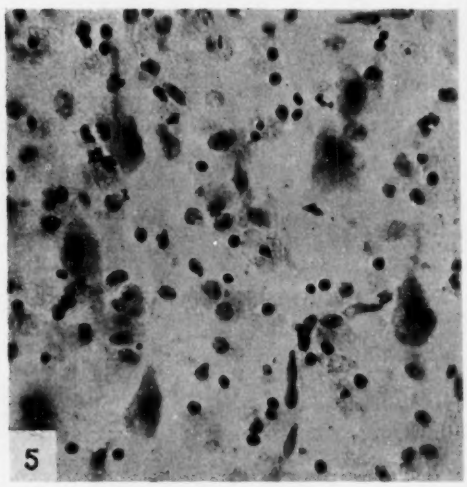
Fig. 2.—Brain after section showing status spongiosus in white matter of frontal pole.

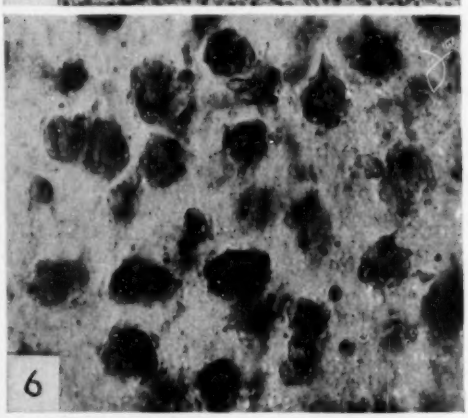
extreme degree of cytoplasmic swelling, feeble staining and ill-defined edges. Bielschowsky staining was not informative, the swollen cell bodies colouring deeply with the silver, but no processes, reticulation, or neurofibrillæ being shown. Staining with Scharlach R. or Sudan III revealed the presence of large amounts of closely packed fine granules of pink or yellowish-red colour in these distended cells. The most conspicuous cell element of the cortex, however, and one that gave an unusual appearance to all areas examined, will now be described. Scattered in varying concentration throughout the outer part of the grey matter and forming a dense band in the deeper third of the cortex were large cells 13 to 20μ in diameter, usually round in shape but occasionally of irregular contour. Numerically they greatly exceeded the obvious nerve cells described above. Cresyl violet stained their cytoplasm with a variable degree of intensity, usually in a uniform manner, but occasionally with a suggestion of granularity in the peripheral portion (Fig. 3). Lipoid stains showed them to be completely filled with fine granules colouring in the same manner as those of the nerve cells (Fig. 4). No processes or neurofibrillæ were demonstrable. Their nuclei, which differed from those of neurones or astrocytes, varied considerably in size and shape, stained darkly, were generally somewhat eccentric in position and often situated at the edge of the cell. A large, round nucleus about 7μ in diameter was the most frequent type, though polygonal, small round and irregularly oval forms were common. In the main these irregularly shaped nuclei appeared shrunken and pyknotic with crenated edges and small peripheral nodules and excrescences, and they occasionally took the form of tortuous deeply staining rods or threads. Two nuclei were sometimes present in one cell. Rarely, a single centrally placed chromatin granule suggested a pathologically altered nerve cell nucleolus. These peculiar cells were absent from the molecular layer and white matter and were exclusively found in areas normally occupied by nerve cells. Their size did not vary with their position in the cortex either as regards lamina or cortical area: they were as large in the granular postcentral and calcarine areas as in the agranular parts of the frontal cortex. In the hippocampus they formed not only the majority of cells in the area pyramidalis subiculi ($H.E_2$ of von Economo), but also of the granular layer of the dentate gyrus the cells of which, while retaining their cap-like formation, had lost their normal granular appearance and consisted of a thin layer of large lipoid-laden cells. In the molecular layer of the frontal cortex Cajal cells were frequently found. These also showed swelling of the amaurotic idiocy type, but to a less degree than did the nerve cells elsewhere. In addition to the cell types described the cortex also contained numerous small, darkly staining nuclei similar to those commonly seen in immature brains. These were chiefly concentrated in the superficial part of the grey matter and were especially conspicuous in the calcarine cortex.

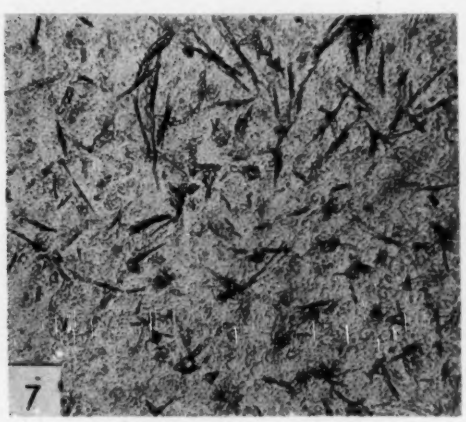
Staining Reactions and Solubility of the Granular Substance.—The granules in the nerve cells and in the peculiar round cells described above had identical histochemical properties. They stained a deep pink or yellowish-red with Scharlach R., less deeply with Sudan III, dark blue with Nile blue sulphate and greyish-black with Weigert's iron hæmatoxylin. Osmic acid did not affect











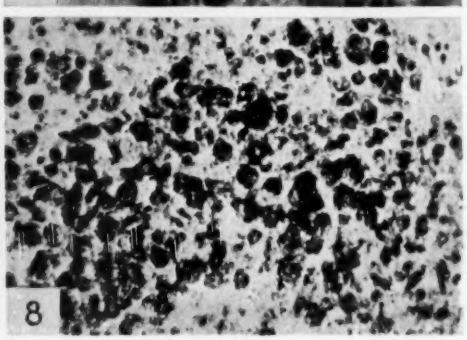


Fig. 3.—Deeper layers of occipital cortex showing rounded, lipoid-laden cells. Cresyl violet. ×180.

Fig. 4.—Occipital cortex. Scharlach R. and Anderson's acid hæmatoxylin after treatment of section with chloroform. ×60.

Fig. 5.—Betz cells showing swelling and loss of Nissl substance. Toluidine blue. ×270.

Fig. 6.—Astrocytes of subcortical white matter showing crystalline deposits and lipoid granules. Scharlach R. and hæmatoxylin. ×360.

Fig. 7.—Extracellular acicular crystals of cholesterol esters in subcortical white matter. Osmic acid. ×100.

Fig. 8.—Focus of heavy lipoid deposition in corpus callosum. Scharlach R. and hæmatoxylin. ×100.

them. Using Anderson's modification of the Kultschitsky-Pal method a black coloration appeared in the cells after 5 days mordanting, though even then differentiation was rapid and the results variable. The granules were not doubly refractile. They were insoluble after prolonged soaking of sections in acetone, methyl alcohol, ethyl alcohol, ether, xylol, pyridine, chloroform or equal parts of ether and methyl or acid alcohol. Boiling chloroform had little effect on subsequent staining save that the granules became more discrete (Fig. 4) and lost a little of their red colour.

Neuroglia.—Astrocytes were proliferated in all layers of the cortex. In the molecular layer elongated bipolar forms were arranged in a roughly vertical manner. In the outer part of the grey matter large fibrillary astrocytes (Fig. 9) sometimes of astroblastic shape (Fig. 10) were attached to thickened arterioles by their sucker feet. In the deeper layers fat-bodied astrocytes with numerous short, wavy processes were the predominant type (Fig. 11). In most of these cells, especially the last, there were present small deposits of yellowish granules resembling those in the nerve cells but less closely packed.

Subcortical White Matter.—Axis cylinders appeared to be absent from all regions of the hemispheres. A great increase in the number of astrocytes was present, the majority appearing as gemästete cells with large oval cytoplasm staining palely with cresyl violet. The nucleus of normal astrocytic type occupied a polar position. While many large fiber-forming cells were present the gliosis was in the main astrocytic not fibrillary in type (Fig. 13). Scharlach R. staining revealed massive lipoid deposition, the whole white matter appearing pink to the naked eye. The cell bodies of the astrocytes were loaded with lipoid granules staining a bright pink. This substance stained greyish-black with the Kultschitsky-Pal method after two days mordanting. It was not doubly refractile and was not blackened by osmic acid. In unstained sections large numbers of extracellular birefringent acicular crystals were seen in the white matter (Fig. 7). In many areas these crystals encrusted the bodies of the astrocytes, sometimes appearing embedded in the non-refractile lipoid contents of the cytoplasm (Fig. 6). Particularly heavy deposits of doubly refractile crystals and droplets formed foci in the deeper parts of the white matter, especially near the ventricle and in the corpus callosum (Fig. 8). In these situations the cell outlines were obscured by the quantity of the deposit. Impregnation methods, however, demonstrated the presence in these foci of phagocytic cells varying in size from that of ordinary compound granular corpuscles to foam cells 30μ in diameter. This anisotropic material had the properties of cholesterol esters. It was readily soluble in acetone. It was darkened by osmic acid and stained deeply with Scharlach and Sudan III. When heated to 50° C. its powers of double refraction were lost, being restored on cooling the section. Chloroform extracts of pieces of the white matter gave a strong Salkowsky reaction for cholesterol, fully equal to that obtained from adult myelinated white matter and far more intense than in control material taken from a normal 14 days' brain. Extracellular droplets of neutral fat were also numerous in the white matter. After treating sections with solvents the bulk of the red staining lipoid disappeared, leaving conspicuous deposits of

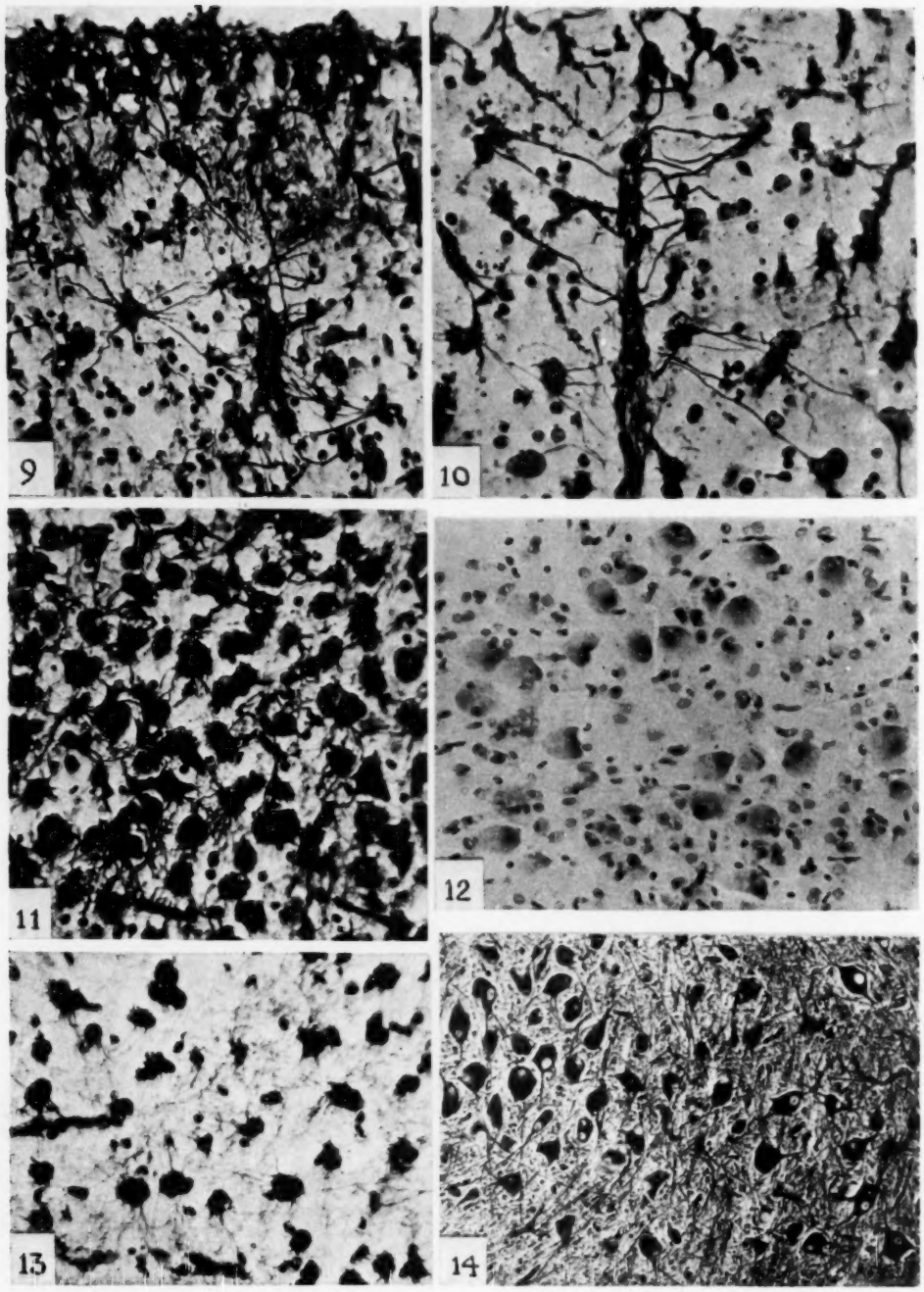


Fig. 9.—Gliosis in superficial layers of cortex. Hortega's method for astrocytes. ×270.
Fig. 10.—Astroblastic cell types in insular cortex. Hortega's method for astrocytes. ×360.
Fig. 11.—Lipoid-laden astrocytes in deeper layers of cortex. Hortega's method for astrocytes. ×270.
Fig. 12.—Nerve cells of thalamus showing swelling of amaurotic family idiocy type. Cresyl violet. ×180.
Fig. 13.—Astrocytes of subcortical white matter with fine fibrils. Hortega's method for astrocytes. ×270.
Fig. 14.—Nerve cells of trochlear nucleus showing swelling. Bielschowsky's method. ×80.

insoluble yellowish-red granules in the cell bodies of the astrocytes. Dense aggregations of nuclei (" germinal centres ") were present in the subependymal region of the white matter.

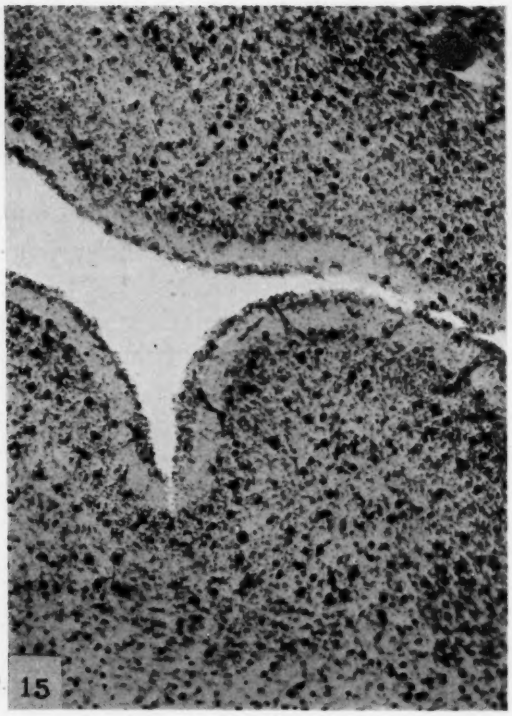
Optic Nerve, Chiasma, and Tract.—There was almost complete absence of myelinated fibres, three or four being present in longitudinal sections of the optic nerve, a somewhat higher proportion in the tract.

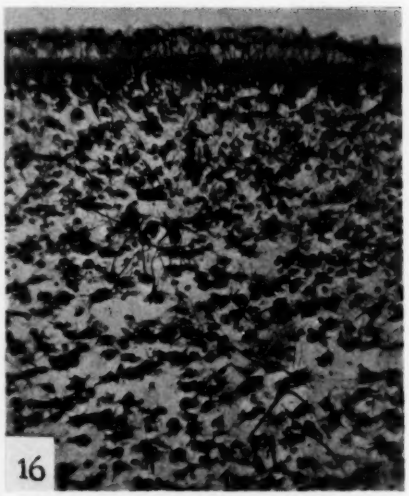
Blood Vessels.—Arterioles showed thickening of the advential layer with proliferation of mesenchymal fibrils. A few yellowish granules were sometimes seen in the vessel walls, but no neutral fat deposits were present.

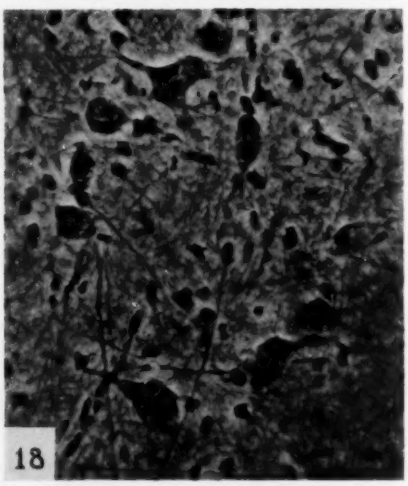
Cerebellum.—Sections made through the vermis and left lateral lobe showed widespread and intense atrophy of nerve cells, the granular layer being recognizable only in a few folia of the anterior part of the hemisphere, the inferior vermis and the flocculus. The molecular layer was extremely narrow and in most areas a well-marked superficial layer of granules was present. Lipoid staining revealed the presence of large, round cells filled with granules scattered throughout the grey matter of the cerebellar cortex (Fig. 15). In the less atropic folia of the flocculus these cells were regularly arranged at the junction of molecular and granular layers. Impregnation methods failed to demonstrate processes save in one or two rare instances where a faint outline of Purkinje dendrites was seen. In its histochemical properties the granular material resembled that found in the nerve cells of the cerebral cortex. The cerebellar cortex was devoid of nerve fibres while the white matter contained only an occasional axis cylinder. Myelin was entirely absent from the cerebellum and its peduncles. No neutral fat was seen in the walls of the blood vessels. There was extensive proliferation of macroglia in all layers (Fig. 16). Swollen glial cells loaded with lipoid were present in the white matter. Extracellular doubly refractile crystals were found with great regularity in the molecular layer and central white matter.

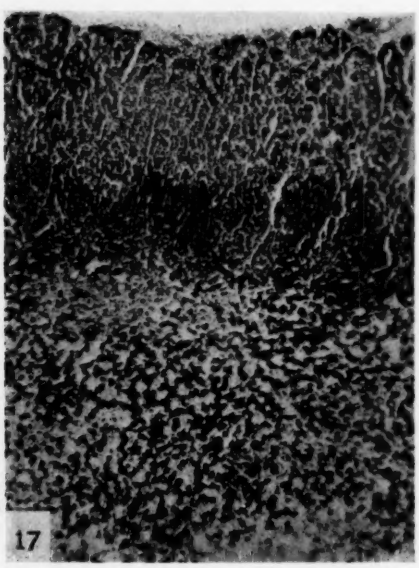
Dentate Nucleus.—The nerve cells showed no numerical loss, but were represented by grossly swollen, round forms filled with insoluble granules, resembling closely the lipoid-laden cells found elsewhere in the cerebral and cerebellar cortices. Holzer staining showed a dense fibrillary gliosis marking the outline of the dentate nucleus.

Basal Ganglia.—Sections made at different levels through the left half of the brain showed a dense cellularity in putamen and caudate nuclei, numerous round cells loaded with lipoid being present. Apart from some of the larger nerve cells it was difficult to distinguish neurones from astrocytes, the staining reactions and insolubility of the granules being the same in both. Selective staining, however, revealed an overgrowth of large astrocytes with little formation of fibres. In the globus pallidus the nerve cells showed great swelling with retention of the normal type of nucleus. Changes typical of amaurotic family idiocy were also found in both thalami where greatly enlarged oval forms with well stained neuronal nuclei displaced to one pole gave a characteristic picture (Fig. 12). Bielschowsky staining showed that most of these cells retained their processes and that the cytoplasm was finely reticulated. There were also numerous rounded forms with few or no processes and a uniform









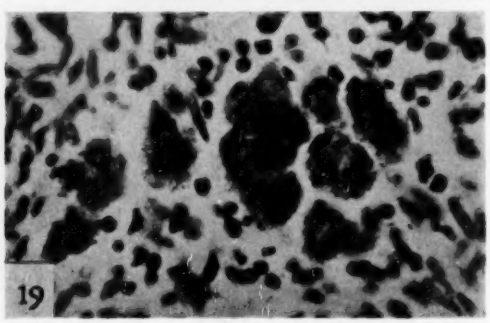


Fig. 15.—Cerebellum. Folia from lateral lobe showing atrophy of internal granular cells, a superficial granular layer and large lipoid-laden cells. Scharlach R. and hæmatoxylin. ×60.

Fig. 16.—Cerebellum. Gliosis in all layers. Extremely narrow molecular layer with proliferated Bergmann glia. Hortega's method for astrocytes. ×180.

Fig. 17.—Suprarenal. Lipoid-laden cells in medulla. Scharlach R. and hæmatoxylin. ×40.

Fig. 18.—Pons. Small nerve cells showing swelling of amaurotic type. Bielschowsky's method. ×270.

Fig. 19.—Spleen. Lipoid-laden phagocytes. Hortega's 1927 method for macrophages. ×450.

dust-like staining of the cell body. Unmyelinated axis cylinders were plentiful. Glial nuclei were increased in number and a heavy fibrillary gliosis was present. The cell bodies of the astrocytes in this situation contained less lipoid than elsewhere in the basal ganglia so that the nerve cells appeared more prominent.

The internal capsule contained no demonstrable nerve fibres and the anterior limb was barely recognizable. The broader posterior limb contained conspicuous deposits of doubly refractile lipoid staining deeply with Scharlach and osmic acid, and a greyish colour with the Kultschitsky-Pal method. Around these deposits, which also occurred in the external capsule, there had developed a coarse network of glial fibres.

Brain Stem.—All the nerve cells showed swelling of the amaurotic idiocy type (Figs. 14 and 18), the large cells of the cranial nerve nuclei in the neighbourhood of the aqueduct being particularly affected. The granular substance found in the neurones stained yellowish-pink with Scharlach and was insoluble in lipoid solvents. Relatively small amounts of intracellular lipoid was sometimes seen in these greatly expanded cells. Swelling in the dendrites was occasionally present in the smaller nerve cells. The nerve cells of the mesencephalic root of the fifth nerve appeared normal. Gross atrophy of the inferior olives was present, only a few round lipoid-laden cells remaining. The olives did not exhibit their normal crenated appearance and were the seat of heavy gliosis. The medullary pyramids were absent. A marked proliferation of fibrous astrocytes was found throughout the brain stem and in the basilar part of the pons a dense fibrillary gliosis was seen in Holzer preparations. As elsewhere, the bodies of the astrocytes contained lipoid granules, but not to the same degree as in the white matter of the hemisphere. Myelin was recognized for the first time in the midbrain and lower levels, but was present in considerably less amount than in control sections made from the brain of a newly born child. The nerve roots of the third, fourth, fifth, seventh and twelfth cranial nerves and a narrow band of fibres emerging from the hila of the olives, were sufficiently well stained to be visible to the naked eye. Microscopic examination showed a feeble myelinization in a minority of fibres in the medial lemniscus, medial longitudinal fasciculus, the dorsal decussation. the decussating fibres of the pontine raphé and in the restiform body. The superior and middle cerebellar peduncles were unmyelinated.

Spinal Cord.—In sections from the short portion of the cervical cord which was available no axis cylinders were seen in the portion normally occupied by the lateral and ventral pyramidal tracts. The dorsal and ventral roots were myelinated. The posterior columns of the cord contained a full complement of nerve fibres, but myelin sheaths were almost absent. Of the remaining tracts, the spino-cerebellar and the fasciculi proprii of the anterior funiculus were sufficiently myelinated to show up without magnification. Elsewhere scattered myelin sheaths were found only on microscopical examination. The nerve cells of the grey matter were all affected by the lipoid change.

Lipoid Abnormalities in the Visceral Organs.—Portions of the spleen, liver, and suprarenals and a few of the mesenteric and para-aortic lymph nodes had fortunately been preserved and were available for examination. In the spleen,

groups of phagocyte cells were found filled with granules having the same staining reactions and insolubility as the nerve cells. These cells averaged 20μ in diameter and had the appearance of reticulo-endothelial macrophages. They did not present the wrinkled surface of Gaucher cells nor the vacuolation of " foam " cells. Groups were occasionally found in the neighbourhood of arterioles in the Malpighian bodies (Fig. 19), but although a conspicuous feature of all sections stained with Scharlach they were not sufficiently numerous to disturb the normal architecture of the organ. The hæmosiderin content of the spleen was not excessive. Similar cells were found in relatively larger numbers in the lymph nodes. The liver was less affected, only the Kupfer cells being involved.

In the suprarenal medulla large numbers of lipoid-laden cells were present (Fig. 17). This lipoid was doubly-refractile and stained a deep red with Scharlach. After treatment with alcohol an insoluble residue of yellowish isotropic granules remained. The lipoid of the suprarenal cortex was not doubly-refractile and after treatment with solvents small quantities of yellowish granules remained in most of the cells.

Discussion

Although from the point of view of nerve cell morphology this case evidently belongs to the amaurotic idiocy group several features distinguish it from the infantile form. The main points of difference are summarized in the table below, the statements made regarding the lipoid abnormalities of Tay-Sach's disease being taken from Hurst's (1925) well-known study.

Elaborating some of these contrasting features one may first draw attention to the insolubility of the granular material present in the nerve cells and glia of our case which more resembles the lipochrome-like substance found in the juvenile form than the prelipoids of Tay-Sach's disease. This extreme insolubility is a property of the nerve cell deposits in Hunter-Hurler's disease (Ashby, *et alia*, 1937), and has been noted in association with tuberose sclerosis in the brain of a year old infant (Norman, 1940). In both these conditions, however, the nerve cell swelling was of the moderate degree found in juvenile amaurotic idiocy, and the astrocytes were not implicated in the process of lipoid storage. There was, moreover, nothing clinically to suggest gargoylism in the present case.

Another peculiar finding was the widespread deposition in the white matter of doubly refractile crystals having the microchemical reactions of cholesterol esters. Chemical tests indicated that the cholesterol content of this unmyelinated " white matter " very significantly exceeded that of a normal brain of similar age and was quite up to the level of normal adult myelinated tissue. Since in the present case these extracellular cholesterol compounds cannot have been derived from myelin breakdown, it must be assumed that they have been deposited from the blood stream, though what factors may have conditioned this phenomenon are obscure. One is confronted with a some-

what similar problem in the Hand-Schüller-Christian syndrome in which, although hypercholesterinæmia may be an important prerequisite, various other local factors of an undetermined character are essential for the massive localized depositions that may occur in the brain (Chiari, 1933). Small amounts of cholesterol compounds may be present in the gitter cells of infantile amaurotic idiocy (Hurst, 1925) and also mixed with the phosphatide in the cell inclusions of Niemann-Pick's disease, but excessive extracellular deposition of the sort found in this case appears to be a unique finding.

TABLE 1

	INFANTILE AMAUROTIC FAMILY IDIOCY	CONGENITAL TYPE
Age at onset	At least 3 months: may be considerably later.	Foetal life.
Size of brain	Well up to average: often unduly massive.	Extreme micrencephaly.
Nerve cells	Marked swelling. Nucleus not often grossly altered. Dendritic swelling frequent and pronounced.	Large numbers of spherical cells with atypical nuclei in cerebral cortex. Dendritic swelling uncommon.
Nerve cell lipoid ..	Phosphatides and cerebrosides. Mostly readily soluble in alcohol and chloroform, but small cells may contain a residue insoluble in acid alcohol-ether mixture but soluble in xylol.	Insoluble. Resists xylol or boiling chloroform.
Neuroglia	Heavy fibrillary gliosis usual.	Gliosis mainly astrocytic.
Neuroglial lipoid ..	Soluble as in nerve cells.	There is a soluble fraction, but the bulk is insoluble as in nerve cells. Total deposition more massive than in Tay-Sach's disease.
Neutral fat	Common in gitter cells and blood vessels walls.	Absent from grey matter. Extracellular droplets in white matter of hemisphere.
Cholesterol esters ..	Small amounts sometimes seen in gitter cells (chiefly perivascular).	Heavy extracellular crystalline deposits throughout white matter of cerebrum and cerebellum. Often seen in cell bodies of astrocytes and phagocytes in white matter.

One of the more difficult points of histological interpretation met with in this case concerned the identity of the numerous rounded lipoid-laden cells of the cerebral cortex. While some of these closely resembled the phagocytic form of microglia, the large size and bizarre variations in shape of the nuclei in the majority were not at all characteristic of compound granular corpuscles. Moreover, the absence of any concentration of these cells around blood vessels

or in the meninges gave no support to the view that they were endothelial macrophages. In Niemann-Pick's disease, Hassin (1930) has drawn attention to the difficulty in distinguishing between some of the spherical inflated nerve cells with pyknotic nuclei and gitter cells, the neutral fat droplets of the latter often being the sole reliable criterion. The cortical cells of our case, however, contained no neutral fat and despite their atypical nuclei it is difficult to avoid the conclusion that these apparent phagocytes are, in fact, a variety of nerve cell the modified structure of which has been conditioned by the fœtal onset of the lipoidosis. That these cells are neurones is strongly suggested by their exclusive localization in the grey matter, their uniform distribution in the ontogenetically older layers of the cortex, their great numerical preponderance over less altered nerve cells, and the similar histochemical reactions of their granular contents to that of undisputed nerve cells in other parts of the brain. Nor is the occasional presence of two nuclei hard to reconcile with this view since multinuclear nerve cells are not uncommon in many different pathological conditions arising in early life. The lipoid abnormalities of Niemann-Pick's or Tay-Sach's disease affect nerve cells which have attained some degree of post-natal maturity, and it is not surprising to find less differentiated and more distorted cell forms in the earlier variety of lipoidosis described here. The same line of reasoning may be applied to the large round cells of the cerebellar cortex which also are reminiscent of those found in Niemann-Pick's disease (Schaffer, 1930), though the insolubility of their granular contents and the absence of lipoid in the walls of the blood vessels are points of difference between the two conditions. The regular arrangement of many of these cells at the junction of molecular and granular layers leaves little doubt that they were Purkinje neurones. Those of similar appearance scattered throughout the atrophic granular layer may be regarded with some justification as heterotopic examples of the same cell type since the general configuration of the cerebellum, its stunted gyri, and the retention of the fœtal superficial layer of granules indicate a retardation in development in addition to the obvious atrophy of the organ.

The fœtal onset of the lipoidosis may also have played an important part in the production of the extreme micrencephaly. Since the rapid increase in weight of the normal brain during early life is largely due to myelinization it would seem likely that the extensive arrest of this process found in the present case was responsible at least in part for the small size and weight of the brain. It is not easy to reconcile this theory, however, with the pathological findings in Tay-Sach's disease in which the brain, though often grossly defective in myelin may yet attain abnormally large dimensions. In one of Bielschowsky's cases the brain weighed 1,690 gm. and that recorded by Steegmann and Karnosh (1936) reached the figure of 2,300 gm. Possibly the great proliferation of neuroglial fibres found in such large brains (as in the case of Holmes, 1911) may account for this excessive weight. In Steegmann and Karnosh's case it was observed that the head increased considerably in size during the last eight months of life. In our congenital form time was presumably lacking for the production of a fibrillary gliosis of such magnitude.

In Tay-Sach's disease much of the myelin deficiency is due to demyelinization of incompletely developed sheaths (Bertrand and van Bogaert, 1934), though a coincident arrest of myelinization is no doubt an associated factor. In our case it would appear that the latter process was the more important. The almost complete absence of myelin in the posterior columns of the cord which contained, nevertheless, a full complement of axis cylinders is particularly remarkable, since this fibre system is normally conspicuously myelinated at birth. Such abnormalities, whether resulting from lack of formation of myelin or malnutrition of pre-existing sheaths have been attributed by Bielschowsky to a disturbance of the normal lipoid metabolism of the glia. In this respect Tay-Sach's disease has much in common with the juvenile form of diffuse sclerosis described by Scholz (1925) and by Bielschowsky and Henneberg (1928). In this connection it may be pointed out that the widespread glial proliferation present in our case cannot be regarded as secondary to myelin degeneration, and would appear to be as much a primary feature of the disease as is the nerve cell swelling.

A further similarity with the infantile form of amaurotic idiocy is seen in the severe atrophy of the cerebellum, especially in its granular layer. Though commoner in the late infantile form this special involvement of the cerebellum has been often noted in Tay-Sach's disease (Westphal, 1917; Dollinger, 1919; Bielschowsky, 1921; Globus, 1923; Ostertag, 1925; Steegmann and Karnosh, 1936). The advanced olivary atrophy found in our case is, however, distinctly unusual.

In this discussion we have stressed the fœtal onset of the pathological process as accounting for many of the peculiar features of this brain. To what extent the lipoid abnormalities of Tay-Sach's disease antedate the onset of the clinical symptoms it is impossible to say. The fact remains, however, that in the great majority of cases no untoward signs are observed until at least three months of postnatal life have elapsed. In the unique case described by Ostertag (1925) pachygyria and microgyria of the cerebral cortex were present, but as the pathological findings were in other respects typical of the infantile form it would seem likely that the malformation was coincidental. In our case the delayed convolutional development of the frontal lobes was not associated with the microscopical picture of pachygyria.

In conclusion it may be said that although in many respects this congenital case has affinities to the infantile form, there are more points of contrast than of similarity. In particular, the insolubility of the intracellular granular inclusions weigh heavily against the view that one is dealing here merely with a forme fruste of Tay-Sach's disease. While the family history of this isolated case gives no suggestion of a genetic origin for the condition, we feel justified in applying to it the name " congenital amaurotic family idiocy," thus drawing attention to its relationship to the other members of this group of lipoid dyscrasias.

Summary

An unusual form of lipoidosis is described in an 18-day old female infant, dying from bilateral hæmorrhages into the renal pyramids. At postmortem the brain was found to be considerably reduced in size and weight (87 gm.) and there was retarded convolutional development in the frontal lobes. Microscopically the nerve cells showed swelling of the amaurotic family idiocy type, the intracellular lipoid being resistive to solvents. Numerous atypical nerve cells showing extreme distention with this material were present throughout the cerebral and cerebellar cortices. Lipoid abnormalities were conspicuous in the glial cells, myelinization was retarded throughout the nervous system, and heavy deposits of extracellular doubly-refractile crystals of cholesterol esters were present in the white matter of the hemispheres and cerebellum. There was a severe olivocerebellar atrophy.

Microscopical examination of the viscera showed evidence of lipoid storage in the reticuloendothelial system, the histochemical reactions of the deposited substance resembling those of the nerve cell granules.

Several points of difference between this condition and Tay-Sach's disease are discussed, and it is concluded that the case is a hitherto undescribed variety of lipoidosis for which the name "congenital amaurotic family idiocy" is suggested.

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IMPERCEPTION FOR THE POSITION OF THE EYELIDS ON ONE SIDE

BY

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Introduction

THE concept of the body schema in its present form originated from the investigations of Head and Holmes (1911–12) into sensory disturbances from cerebral lesions. They showed that appreciation of posture and passive movement requires a " standard against which all subsequent changes of posture are measured before they enter consciousness." For this fundamental standard they introduced the term schema or postural model of the body. They came to postulate a similar schema for the localization of stimuli applied to the body surface. These schemata they supposed to be formed by the past sensory impressions.

Claude (1909) assumed that mistakes in localization and estimation of posture can be caused by the disturbance of certain " mnestic centres for the topo- and kinæsthetic impressions and for the representations of the different parts of the body." Jones (1910) suggested an amnestic disturbance of the association between the sensory perceptions and the " autosomatognostic group of memory feelings " for his cases of allochiria. Pick, who had spoken of " spatial images of the body " (1908), adopted the term schema and stated that these schemata together with the optic image of the body are the essential framework for the consciousness of the body (1915). Earlier theories (Hartmann, Mach, Wernicke, Wundt) of the knowledge one has of one's own body have been summarized by Zingerle (1913). Schilder (1923, 1935) extended the concepts of Head and Holmes and of Pick. His " body schema " (or " body image ") is a complex built up by many somatic factors, among which the postural, kinæsthetic and tactile, as well as the optic and vestibular impressions are the most significant. The body schema contains the representations of the different parts of the body and their spatial relations to each other.

The idea of the body schema has proved indispensable for the understanding of a variety of neurological and psychopathological conditions. In this paper it is proposed to deal with the group of body schema disorders that is most widely known as " anosognosia." This term was originally introduced by Babinski (1914) for cases of left hemiplegia who were completely unaware of and even denied the paralysis, no matter how often one had tried to convince

them of the defect. Babinski's patients seemed to have altogether forgotten the paralysed limbs. F. Müller (1892), Pick (1894), and Anton (1896, 1899) had been the first authors to draw attention to cases of hemiplegia with imperception for the motor loss. The term " Anton's symptom " was used for unawareness of hemiplegia as well as for unawareness of cortical blindness or deafness. The term anosognosia applies only to imperception of hemiplegia, although it could be taken to imply lack of recognition of disease in general. A great number of cases has since become known. The many different interpretations and classifications may justify an attempt to define the main characteristics of the condition as reported in the literature.

Imperception for One Half of the Body

It has often been assumed that the unawareness of the paralysis and the lack of attention for the paralysed side are due to affective reasons. The conscious or unconscious tendency to forget or minimize the disability was believed to account for anosognosia and amnesia for the half of the body involved. But it has become increasingly evident that the disappearance of the affected side from the patient's consciousness is the fundamental disorder and is the immediate result of the cerebral lesion. The patient does not know that he is paralysed, because he has no knowledge of one half of his body. Only secondarily do psychological processes, such as repression and projection, enter into the formation of the symptom. " The psychological factor determines the final shape of the imperception of part of the body " (Schilder, 1935). In the majority of these cases there is a more or less pronounced hemihypoæsthesia which could be taken to explain the condition, if on the other hand there were not a great number of cases that do not show any appreciable sensory impairment. That a patient does not notice his paralysis and does not show any interest in the paralysed side as a whole can therefore only be attributed to a disorder of the body schema. Some of the patients who appear to overlook and never spontaneously use one side of the body are not even paralysed. This was first described by Bruns (1897). Oppenheim (1913) reported a case of right parieto-occipital tumour with apparent hemiparalysis and hypoæsthesia, where the presumed motor and sensory loss vanished when the patient's attention was stimulated. Such cases, showing amnesia for one side without there being any real disability, provide definite proof that in cerebral lesions the disappearance of one half of the body from consciousness is not the result of a repressive tendency. Schilder speaks of " organic repression." It may be less ambiguous to state that these are instances of an organic lesion and mechanism giving results similar to those of a psychological process. This organic counterpart to repression shows how close is the analogy between psycho-analytic concepts and biological facts.

Among the cases of one-sided body schema disorder one can distinguish a class that does not exhibit anosognosia in its stricter sense. Instead of ignoring the paralysis and the affected side of the body, these patients complain that they have lost the arm or the leg. Some observers, e.g. Stockert (1934, 1936), have

assumed an important difference between this class and true anosognosia, maintaining that these patients are conscious of their defect. Closer scrutiny, however, reveals that this consciousness is but a very limited one. Such patients may at times be aware of the paralysis, but for the most part they do not show full insight into the cause of the disability. They have only a vague feeling of a disturbance which they attribute to a complete loss of the limbs. It seems that the affected half of the body does not as completely escape their attention as in cases of anosognosia; but knowledge of that side is grossly impaired and distorted. One is therefore justified in assuming that the difference between these two types of body schema disorder for one side is a difference only of degree. This opinion finds support in the patient whose anosognosia changes into, or alternates with, the feeling that his limbs are absent. Such a development is shown in cases reported by Ehrenwald (1931), Hagen and Ives (1937). Moreover, when patients belonging to either type are made to touch or view the affected half of the body, exactly the same reaction may be elicited: they declare the paralysed limbs are not their own, but someone else's arm or leg.

These facts argue with equal strength against the distinction made on different grounds by Nielsen (1938). This author maintains that in anosognosia the patient has forgotten only the paralysis, not the paralysed side as a whole, whereas " delusion of absence of the limbs " is to be considered as a severe form of amnesia for one half of the body. As early as 1918, in the discussion that followed Babinski's second report on cases of anosognosia, it was stated by Pierre Marie that this symptom is not an independent phenomenon, but belongs to the group of cases who have no idea of the existence of the paralysed half of the body.

The disturbance of the schema of one half of the body is the cause of anosognosia as well as of feeling of absence of one side. The best term for this body schema disorder seems to be the one used by Schilder (1935): imperception for one half of the body. The term anosognosia ought to be restricted to cases where the imperception results in unawareness of the hemiplegia. The other main type of imperception for one side is the feeling of absence of the limbs. This merely descriptive term is to be preferred to " delusion of absence." It will be shown later that only part of the symptom can be called a delusion.

Hemiplegia with Phantom Limb

The foregoing remarks are intended to show that there is no essential difference between unawareness of hemiplegia and feeling of absence of one half of the body. There seems, on the other hand, to be a fundamental distinction between the two types of imperception for one side and the cases of hemiplegia with a phantom limb. Imperception for one half of the body is the expression of a disorder of the body schema. The patients may in addition show loss of sensation, but this is not an essential. In the case of anosognosia patients ignore the paralysis believing they are able to move the limbs, but they have not the vivid impression of a phantom limb. The latter phenomenon is

the expression of the persistence of the body schema, which is merely cut off from the periphery either by actual loss of a limb or by loss of sensation. Thus the body schema remains fixed according to the former state of the body. All cases of hemiplegia with phantom limb show more or less complete anæsthesia. Loss of sensation, especially of the postural sense, is an essential condition for the development of a phantom limb. It explains the phantoms in peripheral nerve lesions (Head; Lurje, 1936; Riddoch, 1937); in lesions of a nerve plexus (Mayer-Gross, 1929), in affections of the posterior roots and columns (Riddoch, 1937), in complete division of the spinal cord (Riddoch, 1917; Stein, 1929; Lhermitte and Tchehrazi, 1937), as well as in certain cases of hemiplegia (Pinéas, 1932).

Cases of hemiplegia with phantom limb are sometimes mistaken for cases of anosognosia, and vice versa. The difference is most obvious in the patient's attitude towards the affected side. The hemiplegic with a phantom limb may at times believe in its reality and forget his defect, but he will always try to make sure by touching or looking at his paralysed arm or leg. He will thus recognize the unreality of the phantom sensation. The anosognostic patient, who has lost all knowledge of the affected half of the body, will not attempt to investigate and may even refuse to look at the paralysed side. He remains unaware of the motor defect and maintains that he can move the limbs, although he never actually tries to move them. When asked to use the paretic arm or leg, he will either move the corresponding limb on the other side or altogether ignore the request. The patient with the phantom limb will sometimes attempt to use it. He then behaves as if he had not lost his limb or its motility. The anosognostic patient, on the other hand, behaves as if the affected limbs had been amputated.

While a sharp distinction is drawn between anosognosia and the phantom limb, it is not intended to deny that the two phenomena show certain analogies. But this applies only to later stages in their development. The gradual involution of the phantom limb follows modifications of the body schema which eventually adapts itself to the new situation. In some cases of anosognosia, e.g. in the first of the two cases described by Pötzl in 1924, the schema of the paralysed side appears to undergo restitution to a certain extent, which leads to phantom formation. These secondary developments do not, however, contradict the view that the phantom limb results from and is evidence for the persistence of the body schema, whereas anosognosia follows its primary reduction.

No attempt is here made to discuss more fully the pathogenesis of the phantom limb and in particular the question of the importance of peripheral sensory stimuli.

The following cases show a symptom that enters into the syndrome of imperception for one half of the body.

Case Histories

Case 1.—R. F., a man aged 55, admitted to hospital on 31st August, 1937. He had been suffering from headaches and paræsthesias in the left hand for three months. One month before admission a left facial palsy had been noticed for the first time. Subsequently he developed headaches localized to the right temple, repeated vomiting, weakness of the left leg.

On admission: Bilateral papillœdema. No hemianopia. Left corneal reflex absent. Left supranuclear facial paresis including the orbicularis oculi. Deviation of tongue to the left. Moderate left hemiparesis with hypotonus. Cutaneous sensation: marked hypoæsthesia for touch, pain, and temperature on the left side of the body including the face. It was remarkable that the patient failed to appreciate the difference in his perception of stimuli applied to the two sides of his body even though on the left he sometimes mistook hot for cold, and vice versa. He was able to indicate the directions of passive movements at all joints, but there was some left-sided ataxia. Left abdominal reflexes absent. Left knee jerk slightly exaggerated. Both plantars flexor.

7th September. Ventriculography: Attempt to reach the right ventricle unsuccessful; the left lateral ventricle appeared well filled with air, dilated and displaced to the left. The subsequent operation (Prof. Schönbauer) revealed a cystic tumour, containing about 50 c.c. of fluid, extending deeply into the white matter of the right central convolutions and the adjoining parts of the right parietal lobe. The tumour was removed as far as practicable. Histological report: mixed spindle- and round-celled sarcoma.

A few hours after the operation the left hemiparesis became complete. On 24th September the following changes were noted: Papillœdema receding. Complete flaccid paralysis of the left side. Almost complete left hemianæsthesia for all forms of cutaneous sensation. From time to time the patient would recognize a pin prick on the face as such, or appreciate both hot and cold stimuli applied to the trunk as "burning hot." Throughout examination he did not show any appreciation of sensory disturbance. Even when his attention was specially drawn to the fact that there was a marked difference in his reactions to stimuli applied to the left side as compared with the right, he would not agree. The sense of posture and passive movement was abolished in all joints of the left arm and leg, with the exception of shoulder and hip joint where it was merely diminished. Left astereognosis.

The symptom to which it is particularly intended to draw attention in this paper was noticed in connection with the left facial palsy, which had after the operation become complete in the lower branch. When the patient was asked to shut his eyes, he could do so for a moment; but immediately afterwards the left eye opened again, whereas the right eye remained shut. When the patient was told to make an effort to keep the left eye shut, he was not only unable to do so, but it also appeared that he did not know that his left eye was open. He said: "But both my eyes are shut," although the left eye was wide open. The following conversation then took place: (Don't you see me?) "No, I don't see you." The patient was directly facing the examiner. (Look more closely!) "Yes, now I can see you." (Are your eyes open or shut?) "My eyes are shut." (Then how are you able to see me?) "I can see you, but my eyes are both shut." (How is this possible?) "Well . . . perhaps the left one is not completely shut, just a little bit open because of the facial palsy." This latter remark is explained by the patient's knowledge of medical terms and suggests that his intellectual powers were intact. It obviously was the result of a compromise between two conflicting sensations, the optic perception and the feeling that both eyes were completely shut.

The patient was then asked to open his eyes, whereupon he opened the right eye, which so far he had kept tightly shut. He now had the sensation that both eyes

were open. When the patient was asked to shut his eyes again, there followed the same sequence of reactions as at the first attempt.

On the other hand, when the eyes were passively closed and the left upper lid was subsequently allowed to open, the patient said at once that he could see and that the left eye was open whereas the right was kept shut by the examiner.

Passive movements of all parts of the face, including the left eyelids, were noticed, their directions recognized.

In the course of the next few months the paralysis and the disturbance of joint sense gradually receded, but there was still marked ataxia. When the patient made his first attempts to walk, he never knew where the left leg was, or when it was time for the left leg to move forward. He could walk without interruption only if constantly told when to move the left leg. Similarly, he did not use the left arm unless especially asked to do so. When he intended to keep his eyes shut, he always had the feeling that both eyes were closed, although the paresis of the left orbicularis oculi was unchanged. There was only this difference compared with his first reactions that he no longer said he could not see when his left eye was wide open.

In February 1938, when the patient left the hospital, the left facial palsy had so far improved that the eyelids covered part of the cornea. He still did not perceive that he could not shut his left eye completely. The movements of the left arm and leg were much improved in the proximal joints, and so were co-ordination and joint sense. The disorder of the cutaneous sensation, however, was only very slightly improved on the whole left side.

Case 2.—J. W., a man aged 45, admitted to hospital on 7th December, 1937, suffering from lobar pneumonia. On 2nd January, 1938, about a fortnight after subsidence of the pneumonia, the temperature rose again. Rhinological and X-ray examination revealed an infection of the right paranasal sinuses.

On 4th January the patient collapsed suddenly; when he had regained consciousness, it was found that he was completely paralysed on his left side. Left ankle clonus. Extensor plantar response on both sides, more marked on the left. Sense of posture and passive movement abolished on the left. Cutaneous sensation: complete anæsthesia on the whole left side of the body including the face (left corneal reflex absent). From questions designed to elicit his appreciation of the sensory difference between left and right it appeared that the left-sided sensory loss was not always noticed by the patient. Fundi normal. Left homonymous hemianopia. Complete paralysis of the left lower face. The power of the left orbicularis oculi was diminished so that the left eyelids gradually opened to a half-way position, whereas the right eye remained shut.

At this stage the patient was asked whether both eyes were shut. He said they were, and to the next question said he could not see anything. When then pressed, he admitted that he could see. (How can you see with your eyes shut?) " Perhaps one of my eyes is not completely shut." (Which eye is open?) " The right one." Asked to point to the open eye, the patient pointed to the closed right eye. Asked to touch the right eye, he did so and realized only now that the left eye was the open one.

It was evident that this mistake was the consequence of the left hemianopia. The remaining right field of vision was referred to the right eye, as is so frequently found in cases of hemianopia. The unusual symptom was the persistent feeling that both eyes were shut while in fact the left was open. Only when he realized that he could see did he conclude that one eye was partly open. This symptom could be demonstrated at all subsequent examinations until, with the gradual improvement of the hemiplegia, the supranuclear facial palsy had receded.

4th January. Blood showed leucocytosis with neutrophilia. C.S.F. clear, globulin tests slightly positive, no increase of cells. The diagnosis of metastatic abscess was made.

2nd March. Encephalography revealed marked dilatation of the right lateral

ventricle and the sub-arachnoid space on the right side, without displacement of the ventricular system.

Case 3.—G. P., a man aged 40, admitted to hospital on 26th July, 1938. Some four years ago, while travelling in a bus that crashed into a tree, he had been hurled against the seat in front of his. No visible injury. He went to bed because of "shock." Nine days after the accident, while in bed, he suddenly felt his left arm and face become weak and numb. This attack lasted for about an hour. Frequent attacks of right hemicrania followed and had persisted. Two months before admission he had two attacks of twitching of the left side of the face at two hours' interval, followed by transient facial paresis. One month later, on awakening, he noticed weakness of his left arm which lasted only two hours. One week before admission he developed a severe headache, and his left arm and leg became weak and numb. Two hours later facial twitching appeared, followed by paresis. The hemiparesis now persisted. The patient complained of headaches and repeated vomiting.

On admission it was noticed that he was unable to keep his eyes shut for more than a few seconds, which was then attributed to lack of concentration. Optic discs: both nasal halves blurred (no obvious papillœdema). No hemianopia. Left facial paralysis of supranuclear type. Marked paresis of the left limbs, more pronounced in the arm, with some spasticity. Cutaneous sensation normal. Joint sense slightly diminished in the left toes. Left abdominals absent. Tendon reflexes increased on the left side. Plantars flexor on both sides.

Lumbar puncture: C.S.F. clear and colourless, with flocculent coagulum. Cells: 35 per c.mm. Total protein 0·04 per cent. Pandy weakly positive, Nonne-Apelt negative. Wassermann reaction negative. X-ray of skull negative.

11th August. The patient still had difficulty in keeping his eyes shut for more than a few seconds. It now appeared that this was due to the left facial palsy which involved the upper branch, though to a lesser degree than the lower: when urged to try hard to keep his eyes shut, he succeeded in keeping his right eye shut, whereas the left upper lid rose slowly until the left eye was wide open. Asked at this stage whether his eyes were closed, the patient's answer was "yes." He did not deny that he could see, but he added that he still felt that both eyes were shut. Left corneal reflex absent. No impairment of the cutaneous sensation of the face. Temperature sense slightly diminished over the left foot. Joint sense diminished in the left fingers and toes.

16th August. Operation (Mr. Harvey Jackson): Right parietal osteoplastic flap. No tumour found. ? Cortical atrophy.

8th September. Ventriculography (Mr. F. H. Masina): Low grade symmetrical hydrocephalus. Ventricular fluid: L. and R. clear and colourless. No cells seen. Globulin tests negative. Protein less than 0·01 per cent.

After the operation the patient was able to keep both eyes closed, although there was still some weakness of the left orbicularis oculi. The other signs of the hemiplegia were also gradually receding. The patient was discharged on 23rd September.

Case 4.—H. C., a woman aged 63. This patient was admitted to the Northumberland Mental Hospital on 6th December, 1935, after having been detained in private mental hospitals under certificate from the age of 39. She had fixed delusions of persecution, and auditory as well as visual hallucinations. Her chief complaint was that snakes and other reptiles were continually assailing and biting her. Her intellectual powers were in no way impaired.

On 12th April, 1940, she had a cerebral hæmorrhage with a few seconds' loss of consciousness. The left arm and leg were completely paralysed. So was the left lower face; she was unable to keep her left eye closed and could not wrinkle the left half of her forehead to the same extent as the right. Left homonymous hemianopia. Left corneal reflex absent. Complete left-sided anæsthesia, including the face. Sense of posture and passive movement abolished in all joints of the left side. Passive

movements of the left eyelids were not perceived. Left abdominals absent. Left tendon reflexes diminished. Extensor plantar response on the left side.

When the patient had regained full consciousness, she did not know what had happened to her. Asked whether she could move her left arm, she first said " yes." Asked for her left hand, she moved her right hand to the left shoulder and then appeared to search for her left hand at the level of the elbow. When she eventually got hold of her left hand, she asked: " Is it here? " She now realized she could not move it.

When she intended to keep her eyes shut, she did not notice that the left upper lid was gradually rising, leaving the eye almost completely uncovered. Asked whether she could see the people around her, she first denied it; but when the test was repeated later in the day, she admitted that she could see although the feeling persisted that both eyes were shut.

On the next day the patient said: " I cannot believe I have an arm. Have you taken it off? I had a terrible shock this morning when I touched my left hand; I thought it was the head of a reptile." Asked where her left arm was, she said: " I don't know. Where is it? I don't feel it." When she had found her left hand by groping along the arm from the shoulder downwards, she exclaimed: " That is someone else's hand. Whose is it? It is not mine. It is a reptile." Only by comparing closely the left thumb with the right did she recognize the left hand as her own. She still said: " It does not feel as if it were mine. It is dead. Is it really my own arm? What has happened to it? "

During the following days she began to realize that she had been paralysed by a stroke and that it was difficult for her to keep the left eye shut. She complained repeatedly that her left arm, and to a lesser degree her left leg, felt dead and queer. " They must be my own because they hang on to my body, but they feel strange." At times, mainly at night or in the early morning, she would tell a nurse that a corpse was lying in her bed at the left side, or that " a poor dead devil's arm " had been put in place of her own.

The left hemianopia had receded completely, but the patient did not pay much attention to objects in her left visual field. At the stage when the left eye no longer opened spontaneously, it could still be shown by separating the lids with the finger that she did not perceive their position. When the left eye had thus been opened, she would either say: " Both my eyes are shut; I can see through the lids," or " The left eye feels as if it were shut, but I know it must be open because I can see and I definitely feel that the right eye is shut." Conversely, when her eyes were open and the left was closed by the examiner, she still believed both eyes to be open.

About a fortnight after the apoplexy motor and sensory function began to improve. The return of cutaneous sensation was accompanied by mistakes in localization: on the left side most of the stimuli were felt nearer the median plane in the same segment; sometimes pin-pricks applied to the left side of the trunk were even referred to the right, close to the middle line, the disturbance thus approaching full alloæsthesia. Her left limbs still felt strange, but this disturbed her less. When making the first attempts to walk, she sometimes complained that she did not know the position of her left leg. She would then ask: " Where has it gone? " When her left eye was opened, she could tell at once that it was open; but she admitted that she knew this only because she could see. Confirmation was to be found in her continued inability to tell when the left eye was passively closed. The persistence of this symptom was the more striking as the cutaneous and deep sensation of the face was then much improved: the patient could feel the examiner's finger on her left eyelids and could even at times indicate the direction of passive movements of the lids.

Discussion

In these four cases of left hemiplegia with involvement of the orbicularis oculi it was found that the patients had no knowledge of their inability to keep the left eye closed. When they tried to keep both eyes shut, and the left eye had opened again whereas the right eye remained shut, they had the feeling that both eyes were shut. In three of the four cases the patients even denied that they could see. Only when questioned more closely, or after repeated experiments, did they admit that they could see, although they retained the impression that the left eye was as completely shut as the right. They then tried to explain the paradox by assuming that the left eye was not quite shut, "just a little bit open," or in one instance by saying, "I can see through the lids." The subjective feeling that both eyes were shut persisted even later on when the patients had become aware of the paresis of the left eyelids. Further proof of the fact that the described symptom contains more than unawareness of a motor defect was to be found in case 4. When this patient had regained sufficient power to keep her left eye shut, it could be opened by the examiner without her noticing that the eye was now open. Moreover, when her eyes were open and the left was passively closed, she thought both eyes were still open. The question whether both eyes were open or shut was always answered in terms of the right eye. This makes it clear that the essence of the symptom is an imperception for the position of the left eyelids, which results in unawareness of a motor defect, but may be present independent of whether there is paralysis or not.

When we come to analyse this disturbance, we have to note that all cases showed varying degrees of sensory impairment. The left corneal reflex was absent in all four cases. But case 3 had no further sensory loss in the face. Case 4 remained unaware of the position of the left eyelids even when all forms of facial sensation were improved. In case 1 the left-sided anæsthesia was almost complete, but there was no loss of sensation for passive movements of the eyelids. These facts lead to the conclusion that the inability to appreciate the position of the lids is essentially independent of the state of cutaneous and deep sensation.

In three of the four cases the sensory examination by itself revealed, in addition to the more or less marked loss of sensation, signs of disturbance at a higher level. The first patient did not notice his severe hypoæsthesia, which he persistently refused to acknowledge. Case 2 showed a similar, though less constant, anosognosia for the sensory loss. In case 4 the displacement of sensory stimuli towards the right side of the body, sometimes tantamount to alloæsthesia, was very similar to mistakes in localization described by Kramer (1915), Van Bogaert (1934), Nielsen and Sult, Jr. (1939), in cases of imperception for the left side due to disorder of the body schema. It thus appears that ignorance of whether the left eye is open or shut belongs to the larger syndrome of imperception for the whole left side of the body. In case 3 this disorder of the body schema was limited to the eyelids; no other sign of disorientation for the left side could be found. Cases 1 and 2 show the symptom of the

eyelids together with imperception of the left hemianæsthesia. These two patients had no anosognosia for the hemiplegia. Amnesia for the left limbs, however, was found in case 1: even when the paralysis had to a certain extent receded, the patient did not spontaneously use his left arm or leg. In case 4 imperception for the position of the left eyelids was part of a complete left-sided imperception in the form of feeling of absence of the limbs. The patient said her left extremities felt queer, as if they were not her own; she thought she had lost her left arm, that it was someone else's arm, the arm of a corpse, or even that it was a reptile. This latter illusion fitted so closely into the delusions the patient had been voicing for many years, that it might have been attributed to her mental disorder. But the snakes and other reptiles by which she felt herself tormented had never before been identified with parts of her own body. Further, exactly the same illusion has been observed in patients with imperception for one half of the body who were not suffering from a psychosis. Pötzl (1924) describes the case of an anosognostic patient who said his paralysed arm belonged to somebody else; he would at times look at his left arm with the expression of utmost horror, exclaiming a snake was creeping towards him. Ehrenwald (1931) reported a case of left hemiplegia who, after a period of anosognosia, complained that he had lost his left arm and that it had been replaced by a snake. Delusions that the affected limbs belong to someone else, or that a corpse, stranger, or double lies at the patient's side, are frequently met in cases of imperception for one half of the body. The common feature of all these delusions is the projection of the affected half of the body into the outside world. They are secondary productions, resulting from the patients' feeling of absence of one side and from their inability to recognize their limbs as their own. This agnosia or imperception for one half of the body is the primary symptom; it is the immediate consequence of the cerebral lesion, the expression of organic disorder of the body schema.

Almost identical symptoms have been observed in psychogenic disorders, e.g. in a case of hysterical hemianæsthesia (Bernheim, 1893) and in cases of hysterical dyschiria (Jones, 1907 and 1910). Schilder (1923, 1935) and Ehrenwald (1931) have discussed the relationship between depersonalization and hypochondria on the one hand, and organic disturbances of the body schema on the other. All these conditions show that the function of the body schema can be disturbed by psychogenic processes as well as by cerebral lesions. The resulting symptoms, and probably also the final mechanisms of their production, may in many cases be the same for both psychogenic and organic disorder.

Some authors have stressed the importance of hemianopia and conjugate deviation in the development of imperception for one side of the body. None of the four cases had deviation of either head or eyes. In one of the two cases with left homonymous hemianopia the visual field became normal a few days after the apoplexy (Case 4). It then appeared that the patient paid less attention to objects in her left visual field. This symptom has been noticed in a number of similar cases who had not previously been hemianopic. It seems to be the consequence rather than the cause of the imperception for the left half of the body, which in some cases leads to more or less complete im-

perception for the left half of the external space. Homonymous hemianopia and conjugate deviation towards the normal side do, of course, facilitate imperception for the paralysed side, but they do not appear to be essentials for this condition. A hemianopia may, however, modify the symptom of imperception for the eyelid position, as shown in case 2.

Imperception of paresis of the eyelids, and of their position, due to disturbance of the body schema has not hitherto been reported in the literature. Hofmeister and Meyer (1906) described a case of sarcoma of the right Gasserian ganglion who did not know whether the right eye was open or shut. This was fully explained by anæsthesia of the face combined with complete blindness of the right eye due to secondary optic atrophy. The striking point in the cases reported in this paper was that the patients had no knowledge of the position of their eyelids on one side although they were not blind in that eye. Three of them went so far as to deny that they could see: the feeling that the left eye remained shut led at first to a suppression of its visual perception. This is analogous to the not uncommon finding that a patient with imperception for one half of the body does not know where his arm is, and maintains he has lost it, even when the arm lies in the centre of the patient's visual field (Schuster, 1936). Golman (1935) observed in some cases of infranuclear facial paralysis that the patients were unaware of the motor defect until attention was drawn to it. They all showed disturbance of proprioceptive facial sensation. They had illusions of movement of the paralysed muscles. Golman described this condition as anosognosia. Anosognosia, however, is not the right term for such cases. It is characteristic that the unawareness of the paralysis did not persist after the patients had been told of the motor loss. This type of unawareness of motor defect with illusions of movement corresponds to the transient imperception for peripheral paralysis, hemiplegia, or amputation, in cases with phantom limbs. The essential conditions are the same in all these cases: loss of a limb, or of motility and sensation in one part of the body, the cerebral mechanism that secures the body schema being intact.

In the cases described in this paper, where the unawareness of the eyelid paresis appeared to be caused by a disorder of the body schema, there were no phantom sensations, no motor illusions. The patients had the impression that the left eye remained shut, because they had intended to shut both eyes, and because they correctly perceived the right eye as shut, whereas they had no perception for the actual position of the left lids. For the same reasons do patients with unawareness of hemiplegia more readily believe that they are performing the required movements with the paralysed arm when they are asked to move both arms simultaneously (Pinéas, 1926). The anosognosia can only be maintained because of the underlying imperception for the affected half of the body. Unawareness of paralysis and imperception for one side were in one of the four cases restricted to the eyelids, and in the others there most pronounced. The patients could not tell whether the left eye was open or shut, because they had no knowledge of the position of the left eyelids. Mills (1910) expressed the opinion that the postural sense is not as highly developed for the muscles innervated by the facial nerve as for those of the limbs. His

argument was based on the facts that the sense of position is both a muscle and a joint sense, that the recognition of position of a limb is largely dependent upon impressions received from joints, and that the facial muscles, except, of course, those of mastication, do not perform movements about a joint. Mills concluded that these movements "are probably not to any large extent dependent for their proper performance upon the postural sense, at any rate not to the same extent as joint movements." It is obvious that the movements of the eyelids do not require a precise sense of position. Considering the importance of the postural and kinæsthetic impressions for the development of the body schema, one may well assume that the eyelids are less firmly represented in the schema than other parts of the body. This would explain that imperception for the position of the eyelids on one side can be the most pronounced, and in some cases, as in case 3, the only sign of imperception for one half of the body.

The cases reported in this paper do not lend themselves to attempts at exact localization, for none was verified by autopsy. The full extent of the tumour in case 1 could not be ascertained at the operation; pathology and localization of the lesions in the other three cases can only be surmised. But all the verified cases of one-sided disorder of the body schema show more or less circumscribed lesions of the parietal lobe. The view that anosognosia can be caused by lesions of the corpus callosum has not been substantiated. Cases used to support this localization show lesions extending into the parietal lobe. Some authors place the main stress on lesions in or close to the thalamus, others on lesions of the parietal cortex in the region of the interparietal sulcus and the angular and supramarginal gyri. In the two cases reported by Pötzl in 1924 there were lesions both in the thalamus and at the bottom of the interparietal sulcus. Schuster (1936, 1937), in his "Contributions to the Pathology of the Thalamus," came to the conclusion that the thalamo-parietal system is to be considered as a physiological unity. His view is that a lesion at any point between the thalamus and the parietal cortex can give rise to disorder of the body schema. The body schema disturbance described in this paper can therefore be safely attributed to parietal lesions, a localization that is corroborated by the other clinical symptoms in the four cases and by the site of the tumour in case 1.

These were all cases of imperception for the position of the left eyelids. So also the syndrome of imperception for the complete half of the body has in the great majority of cases been found in left hemiplegia. Some authors tried to explain this fact by attributing to the right hemisphere a leading role with regard to the body schema. Others adopted the view expressed by Hauptmann (1928) that the left hemisphere is of such predominant importance for the body schema that any lesion preventing the sensory impressions from the left half of the body from reaching the left cerebral cortex by way of the corpus callosum will cause anosognosia. But by now a number of cases with imperception for the right side, without any indication of left-handedness, have become known, which warrants the conclusion that the organic substrate of the schema for either half of the body is localized in the contralateral hemi-

sphere. In this respect at least the right hemisphere appears to be the equal of the left. The knowledge of the spatial relations of the different parts of the body to each other and to the body as a whole is lost in bilateral lesions of the parietal lobes (Pick's autotopagnosia). Only the highly specialized functions of the body schema are predominantly vested in the major hemisphere: Gerstmann's finger agnosia and confusion between right and left are caused by lesions at the border of the angular gyrus and the second occipital convolution of the left hemisphere.

A plausible explanation for the prevalence of imperception for the left side has been suggested by Schilder (1935). He points out that there is a physiological tendency in right-handed persons to neglect the left half of the body, and argues that most focal lesions of the left hemisphere will not have the effect of overcoming this tendency, whereas focal lesions of the right hemisphere "added to the physiological tendency to neglect the left side will provoke the picture of non-perception of the left side of the body." In most of the larger lesions of the left hemisphere the aphasia would make it difficult to detect the body schema disorder. A similar opinion had been expressed by Hoff and Pötzl (1931).

The hypothesis that the left side is less firmly represented in the body schema than the right may be supported by an observation made by Tournay (1922). This author found that the infant begins to look at and use the right hand at the age of about four months: only about a month later does it pay similar attention to the left hand. This observation which seems to suggest that in right-handers the knowledge of the left side develops later than that of the right has not yet been verified on a larger scale. It is obvious, however, that in later life far more impressions of all kinds come from the right than from the left hand and arm. As these impressions are the elements by which the body schema is built up, the schema of the left half of the body will never be as well established and will therefore be more easily affected by pathological processes than the schema of the right side.

These considerations do not apply to the eyelids. The movements of the eyelids are exquisitely bilateral and symmetrical. If one eye is shut by itself, the tendency to shut the other eye simultaneously is always revealed by a slight contraction of the orbicularis, and in forced shutting by compensatory action of the frontalis. There is no unilateral dominance with regard to the eyelids. It is therefore possible that imperception limited to the lids may be found in left hemisphere lesions that do not suffice to produce imperception for the whole right side. This remains to be seen, and would be mainly of theoretical interest, for in affections of the left parietal lobe there will be other localizing signs.

The symptom described in this paper may, however, be of some clinical value in affections of the right hemisphere. Nielsen (1938) says: "In the field of cerebral localization there has been great advance in the last 25 years, much of which is not of aid in lesions of the right hemisphere. The syndrome of amnesia or unconsciousness for the left limbs stands out as one of the few definite aids in diagnosis of lesions of the right parietal lobe." In one of the

cases here reported the imperception for the position of the left eyelids was the only sign of body schema disorder. By revealing such a disorder it may in certain cases help to diagnose an affection of the right parietal lobe.

Unawareness of the one-sided sensory loss may have a similar value. Zingerle (1913) was the first to point out that the patient who is unaware of his hemiplegia ignores the hemihypoæsthesia as well. This was confirmed by Barkman (1925). Cases 1 and 2 of this paper showed anosognosia limited to the sensory loss. It is obvious that the latter can more easily escape consciousness than the paralysis. Isolated imperception for the hypoæsthesia seems to be another indicator of one-sided disorder of the body schema.

Summary

It is shown that unawareness of hemiplegia and feeling of absence of the limbs are closely related symptoms, and result from imperception for one half of the body.

A distinction is made between this disorder of the body schema and hemiplegia with phantom limb.

Four cases are described to illustrate a symptom that forms part of the syndrome of imperception for one half of the body: unawareness of whether one eye is open or shut, due to imperception for the position of the eyelids on the affected side.

The pathogenesis and value of this symptom are discussed.

The similarity between organic and psychogenic disturbance of the body schema is emphasized.

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THE LOCAL EXTENSION OF NERVE FIBRES INTO DENERVATED AREAS OF SKIN

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Introduction

THE existence of extensive overlap between the cutaneous nerve fibres derived from successive nerve roots was first demonstrated by Sherrington (1893) in a study of residual sensibility after section of one or more roots. Other methods, such as that involving local strychninization of the dorsal spinal roots employed by Dusser de Barenne (1910), have been found to give essentially similar results. The method of antidromic stimulation (originally used by Stricker (1876) and Bayliss (1901)) and the study of residual sensibility after the section of dorsal nerve roots were both employed by Foerster (1936) to determine the extent of each human dermatome, and again the correspondence between the results obtained by both methods was close.

The amount of overlap which exists between the peripheral cutaneous nerves of the limbs has been determined by a number of methods, which include anatomical dissection, the successive anæsthetization of nerves supplying contiguous areas of skin followed by sensory tests (Woollard *et al.*, 1940), electrical stimulation methods through the intact skin (Thompson *et al.*, 1934), and finally by the analysis of the sensory loss following peripheral nerve injuries in a large series of patients (Foerster, 1917, 1929). The correspondence between the stimulation and anæsthetization methods is reasonably close. On the other hand, the analysis of sensory loss and sweat secretion (Guttmann, 1940) following nerve injuries shows in many cases very large degrees of overlap which are not demonstrated by the other methods. This finding, taken in conjunction with the clinical observation by Pollock (1920) that the areas of sensory loss following nerve injuries shrink circumferentially before any regeneration can have taken place from the central stump, suggests either that the method of recording residual sensibility is not entirely accurate or that a proportion of overlapping nerve fibres do not transmit impulses giving rise to sensations for some time following a nerve lesion (Pollock, 1919). It is also possible that a new growth of fibres from surrounding normal nerves towards the area of sensory loss takes place (Schuh, 1911, and Weddell and Glees, 1941).

The method of staining nerve fibres throughout large whole preparations of skin by local injection of methylene blue (Weddell, 1941) has been applied

to experimental animals in an attempt to determine the nature of the shrinkage in the area of sensory loss which follows section of a peripheral nerve before regeneration from the central stump has occurred. Two of us (L. G. and E. G.) have carried out sensory tests (nociceptive) in a large number of rabbits following the division of a variety of peripheral nerves. In general the findings are remarkably constant, and the rabbit as an experimental animal has been found as reliable a subject for observation as man. The data presented here concern the relation of the cutaneous territory of the sural nerve * to those of its adjacent nerves, the tibial and peroneal, and the phenomenon of shrinkage of the area of sensory loss in these areas after resection of either the tibial and peroneal nerves together, or the sural nerve only, before regeneration from the central stump has taken place.

Methods

Two series of rabbits were employed, in each of which different procedures were adopted.

Series I.—In each of 12 rabbits the following operations were performed. Under intravenous nembutal anæsthesia (0·7 c.c./kilo of a 5 per cent. solution of Abbot's nembutal), and after shaving the skin, the sciatic nerves were exposed with full aseptic precautions in the middle third of each thigh in turn. The sural nerve was dissected away from the tibial and peroneal nerves. On one side the sural nerve was divided, and on the opposite side both the peroneal and tibial nerves were sectioned. Portions of both proximal and distal stumps of each divided nerve were resected to leave as large a gap as possible without damage to the remaining nerve or nerves. Next, the remains of the proximal stumps were turned towards their points of origin, and finally the wounds were closed in two layers with interrupted thread sutures. Very shortly after the operation, and sometimes while the animal was still under light anæsthesia, a sensory test (nociceptive) was carried out. In order to conform as closely as possible to a clinical method commonly used in man, the sensory test consisted of needle pricks with a sharp-pointed, round-bodied, 26 S.W. gauge steel needle, working from the area of sensory loss towards the sensitive skin. The needle point was inserted vertically through the whole thickness of the skin at approximately 1–1½-second intervals until the first withdrawal reaction occurred; this spot was then marked on the skin with Indian ink. Occasionally the first reaction of the animal to a prick as the sensitive area was approached was a slight increase in the respiratory rate and increased movement of the nares; the next prick (approximately ½ mm. closer to the sensitive area) was found to cause a definite withdrawal reaction. The first reaction was taken to indicate the boundary of the sensitive area, and this boundary was marked by an ink spot. Immediately following the test, the ink spots which thus outlined the area of sensory loss were tattooed into the skin with an electric tattoo machine. Similar tests were carried out at various intervals following the nerve resection, commencing in many cases on the day following the operation; changes in the area of sensory loss as shown by these tests were also outlined by tattooing ink spots into the skin.

At intervals of 1, 2, 3, 4, and 12 weeks following the first operation, the animals were anæsthetized immediately after a sensory test, and the area of skin supplied by the sural nerve (with a small margin outside) was infiltrated with 0·02 per cent. methylene blue in normal saline solution containing 1 per cent. procaine hydrochloride. This was allowed to stain for three-quarters of an hour, after which the skin and subcutaneous tissues were removed, fixed, and cleared as a total preparation by methods which have been described previously (Weddell, 1941).

* Some authors refer to this nerve as the saphenous minor nerve in the rabbit.

After the skin had been removed the animals were killed and the sciatic nerves exposed at the point of operation to see whether any nerve fibres from the proximal stumps had reached the distal stumps of the resected nerves. In doubtful cases portions of intervening tissue were removed and examined microscopically after silver impregnation (see Table 3).

Series II.—In four rabbits, under nembutal anæsthesia, after shaving the skin and with full aseptic precautions, the sciatic nerve was exposed in the middle third of the thigh on the right side only, and the sural nerve separated from the tibial and peroneal nerves as described above; but in these cases none of the nerves was sectioned, although minimal trauma could not be excluded. The wound was closed in two layers as before. Sensory tests (nociceptive) were carried out on the following day, and at intervals of one and two weeks after operation. In these animals sensory tests consisted of a comparison of the withdrawal reactions on the two sides following pin-pricks; in addition, in order to determine whether any motor fibres in the sciatic complex had been damaged, toe-spreading on either side in response to the abrupt lowering of the animal towards the ground was compared. After periods of one week or two weeks following the operation, skin over the outer side of the ankle on both sides was stained with methylene blue and prepared for microscopical examination. The sciatic nerves in their course through the whole of the thigh were also removed with the greatest care, stained in osmic acid, and examined by serial longitudinal sections. The nerves from both sides were treated exactly alike throughout the preparation of the sections. As a further control the sciatic nerve of one rabbit was exposed in the middle third of the thigh on the right side only, but the three separate trunks were not interfered with in any way. The wound was closed in two layers as usual. The sciatic nerves and skin from the ankle regions were likewise removed from this animal for microscopical examination.

Physiological Observations

After section of the sural nerve only, an area of analgesia, shaped somewhat like a boot, is found to be situated over the lateral aspect of the lower two-thirds

Fig. 1.—The area outlined in Indian ink is analgetic and was obtained immediately after isolated section of the sural nerve.

Fig. 2.—The stippled areas are analgetic. The boundaries were obtained immediately after section of the tibial and peroneal nerves on the left side and the sural nerve on the right side.

of the leg, the lateral part of the ankle, and the proximal part of the lateral margin of the sole and heel (Fig. 1). After section of the tibial and peroneal nerves, the area of remaining sensibility is considerably larger, which indicates the measure of overlap between the sural and its surrounding cutaneous nerves. The overlap is most marked in the sole, where the maximal zone may extend over the greater part of the heel (Fig. 2). The distal extremity of the skin supplied by the sural nerve on the foot ends in the region of the head of the fifth metatarsal, and here there is considerable overlap (Fig. 3). Since the distal

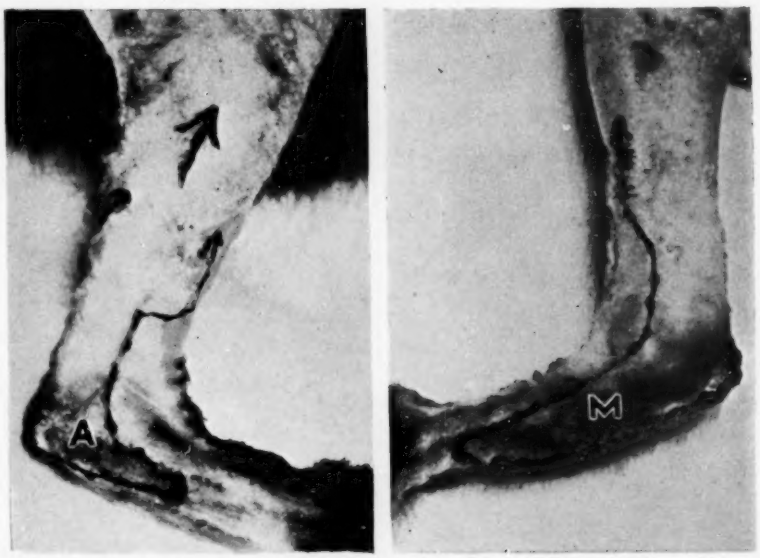

Fig. 3.—The areas outlined were obtained immediately after section of the sural nerve on the left side and the tibial and peroneal nerves on the right side. A = Centre of autonomous zone; M = Centre of maximal zone of sural nerve.

extremity of the area of skin supplied by the sural nerve on the foot is surrounded by skin supplied by the peroneal and tibial nerves only, measurements can be taken from the calcaneum to this boundary both when comparing the relative sizes of the autonomous and maximal zones of the sural nerve and when estimating the shrinkage of the area of sensory loss.

Table 1 is a summary of such measurements made on opposite sides of each animal on the day following operation.

TABLE 1.—SHOWING COMPARISON BETWEEN THE DISTAL EXTENSION OF THE MAXIMAL AND AUTONOMOUS ZONES OF THE SURAL NERVE

CASE NO.	AUTONOMOUS ZONE	MAXIMAL ZONE
	(millimetres)	(millimetres)
9	49	55
18	40	54
19	43	50
22	36	48
27	40	44
539	31	48

A more detailed comparison of the areas of sensory loss on the two sides shows that the overlap from surrounding nerves varies in different regions; in some positions the intermediate zone is large whilst in others it is very much smaller (Fig. 4). The relative size of the intermediate zones remains,

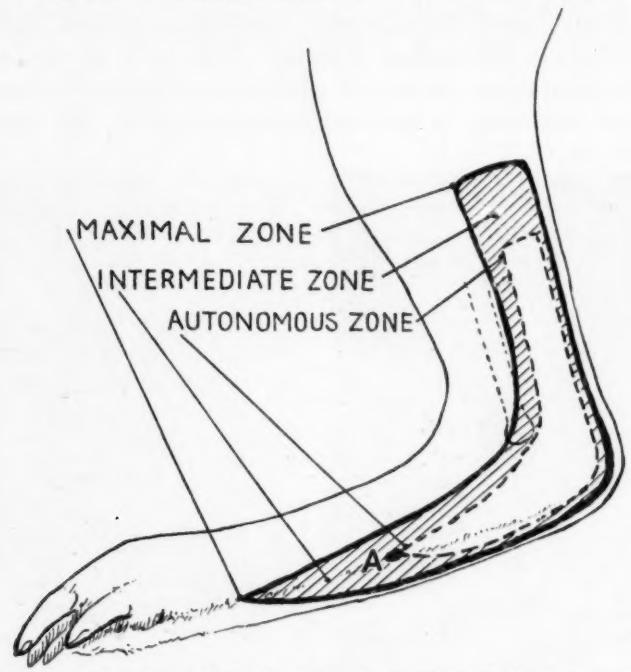

Fig. 4.—Lines representing the outline of both autonomous and maximal zones of the sural nerve have been projected on to a single leg in order to indicate the extent of the intermediate zones. A = base of 5th metatarsal.

however, fairly constant from animal to animal. The intermediate zones are always characterized by a diminished number of spots from which nociceptive responses can be aroused; moreover, the responses are diminished in intensity and often delayed as compared with responses from normal areas of skin. In addition to pin-pricks, faradic stimuli were applied through bipolar electrodes in intermediate zones; the threshold was found in all cases to be raised, but more towards the area of sensory loss than close to normal skin (Table 2). Owing to the diminished number of spots from which sensory responses can be aroused, the boundary line between analgetic and normal skin does not appear to be so sharp as compared with areas in which there is a minimum of overlap.

TABLE 2.—NOCICEPTIVE REACTIONS IN THE AREA SUPPLIED BY THE SURAL NERVE AFTER RESECTION OF TIBIAL AND PERONEAL NERVES

POSITION OF STIMULUS	FARADIC STIMULUS	RESPONSE
Distal extremity of sensitive zone ..	Coil 6·5 cm.	Diminished and sometimes delayed.
Level of base of fifth metatarsal ..	,, 7·2–10·3 cm.	Diminished.
Just below external malleolus.. ..	,, 11 cm.	Brisk, maximal.

There was never at any time any excessive nociceptive response in rabbits comparable with that which can occasionally be aroused from intermediate zones in man.

Diminution of the Area of Sensory Loss.—Shrinkage of the area of sensory loss was found to take place after isolated section of the sural nerve. The shrinkage is most marked in the neighbourhood of extensive intermediate zones, but is not entirely confined to such areas. The results of sensory tests 1 and 17 days following isolated section of the sural nerve are seen in Fig. 5.

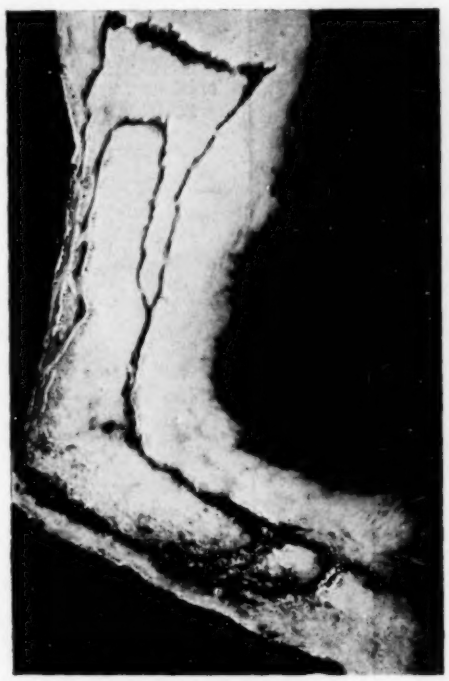

Fig. 5 shows the outline of the areas of sensory loss 1 and 17 days after isolated section of the sural.

Fig. 6 shows the outline of the areas of sensory loss in the sole 1 and 17 days after isolated section of the sural nerve. (Compare fig. 2.) The stippled areas are analgetic.

The shrinkage commences in some cases as early as the day following operation (Table 3). It is also clear that following section of the tibial and peroneal nerves there is a steady extension of the maximal zone of the sural nerve; the amount of the extension in one case 17 days after section of the tibial and peroneal nerves is shown in Fig. 6. The character of the response to pin-prick within such zones of shrinkage or extension is in every case similar to that obtained in intermediate zones immediately following operation.

In order to compare the changes in the extent of the autonomous and maximal zones of the sural nerve at various intervals following operation, measurements from the calcaneum to the distal boundary marking the limit of the area of sensory change have been tabulated (Table 3).

In rabbit No. 539 nerve fibres from the proximal stump of the sural nerve had reached the distal stump and regeneration through the distal stump had

taken place. The rapid shrinkage in the area of sensory loss between the 84th and 91st days presumably coincided with the arrival of fibres from the proximal stump.

TABLE 3.—CHANGES IN THE EXTENT OF THE AUTONOMOUS AND MAXIMAL ZONE OF THE SURAL NERVE. MEASUREMENTS FROM THE CALCANEUM TO THE DISTAL BOUNDARY OF SENSORY CHANGE

RABBIT NO.	TIME OF TEST	EXTENT OF AUTONOMOUS ZONE	NERVE FIBRES IN DISTAL STUMP (SURAL NERVE)	EXTENT OF MAXIMAL ZONE	NERVE FIBRES IN DISTAL STUMPS (TIBIAL AND PERONEAL NERVES)
		(MILLIMETRES)		(MILLIMETRES)	
18	(1) Immediately after operation	40		54	
	(2) 21 days after operation..	23	0	57	0
19	(1) Immediately after operation	43		50	
	(2) 1 day after operation ..	43		50	
	(3) 18 days after operation..	35	0	56	0
22	(1) Immediately after operation	36		48	
	(2) 1 day after operation ..	30		50	
	(3) 26 days after operation..	Small patches of analgesia.	0	56	0
539	(1) 1 day after operation ..	31		48	
	(2) 5 days ,, ,, ..	27		48	
	(3) 17 ,, ,, ,, ..	27		48	
	(4) 30 ,, ,, ,, ..	27		51	
	(5) 47 ,, ,, ,, ..	23		51	
	(6) 84 ,, ,, ,, ..	23		51	
	(7) 91 ,, ,, ,, ..	18	+	52	0

In the rabbits in which the sciatic nerve had been exposed on the right side only, and the sural nerve merely separated from the tibial and peroneal nerves, sensory tests (nociceptive) on the day following operation showed that there were a diminished number of spots from which withdrawal reactions could be obtained over the area of sciatic distribution on the operated side as compared with the normal side. In addition the toe-spreading reaction on the operated side was not as wide as that on the unoperated side, suggesting that some motor fibres had also been damaged. One week after operation the changes were far less marked, and at the end of two weeks less marked still, though in all cases some slight difference between the two sides could be detected in favour of the unoperated side. There was great individual variation between the results obtained in different animals in this series, so that it was not possible to make a statistical analysis. In the one animal in which the sciatic nerve had only been exposed, however, no difference in sensory responses or toe-spreading

reactions could be detected between the two sides, either on the day following or one and two weeks after operation.

Histological Observations

Series 1. *Maximal Zone of the Sural Nerve.*—The pattern of innervation in the area of skin supplied by the nerve was found to bear a general resemblance to that already described in the ear of the rabbit (Weddell, 1941). There is centrally placed a proximo-distally running nerve trunk, from which spring subsidiary nerve trunks, giving rise to bundles which scatter in all directions beneath the skin to enter the cutaneous nerve plexus. As in the case of the

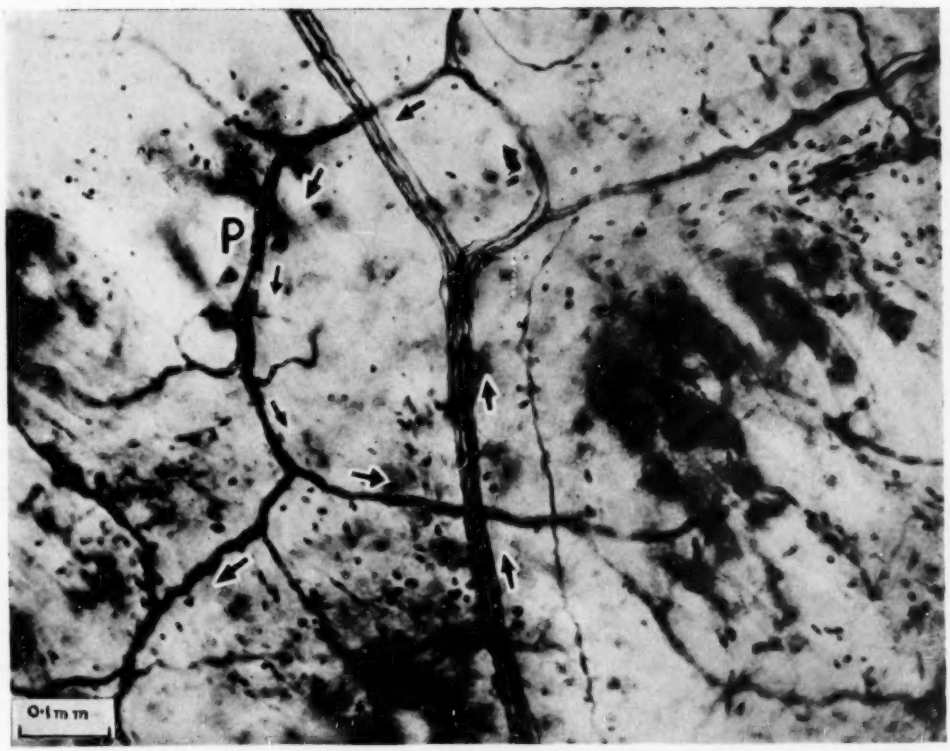

Fig. 7 shows a peripherally running nerve bundle within the maximal zone of the sural nerve which gives rise to fibres entering the cutaneous nerve plexus, the majority of which proceed centrally and superficially towards the skin. The arrows indicate the direction along which the fibres from the nerve trunk are passing. P=cutaneous nerve plexus. The illustration is from a methylene blue stained preparation taken from the skin of the leg of a rabbit.

ear, a large number of nerve fibres pass directly to the periphery of the area of skin which they collectively supply before giving rise to fibres which enter the cutaneous nerve plexus and run centrally and superficially towards the skin. In the illustration (Fig. 7) a peripherally running nerve bundle is shown which gives rise to fibres entering the cutaneous nerve plexus and proceeding centrally and superficially towards the skin.

In skin taken from the centre of the maximal zone supplied by the sural nerve one week after section of the tibial and peroneal nerves, there are sometimes as many as twice the number of nerve fibres undergoing degenerative

changes as compared with the skin from the same region of an unoperated animal. Apart from this no morphological changes could be detected. In skin removed from similar areas 3, 4, and 12 weeks after section of the tibial and peroneal nerves, no differences could be seen as compared with skin taken from the same region in an unoperated animal. The general neurohistological picture in the skin of the leg is, however, different from that seen in the ear of the rabbit (Fig. 8). In the leg the great majority of hair follicles are supplied by fibres which lose their medullary sheaths during their passage through the cutaneous nerve plexus. At wide intervals of ½ cm. or more, however, there are large, thick hairs which are supplied by more than one medullated nerve

Fig. 8 shows the neurohistology of the centre of the maximal zone of the sural nerve. The staining of the Schwann sheaths and nuclei is clearly seen. Methylene blue stained preparation taken from the skin of the leg of a rabbit.

fibre. The superficial nerve nets which are situated immediately beneath the epidermis, and from which arise fine beaded terminals ending between and beneath the cells of the deepest layers of the epithelium, are similar to those seen in skin from the ear of the rabbit, and a similar interlocking between the nets is apparent. The fact that the majority of fibres of the cutaneous nerve plexus are non-medullated can be readily seen in these preparations because the blue staining of the Schwann sheath and nuclei which invariably occurs after methylene blue staining in this region makes it possible to affirm the absence of a medullary sheath (Figs. 8 and 9). The axis cylinders within the sheaths are often so fine that, owing to the deep staining of the sheath, a proportion

of them can no longer be seen. Before entering and on leaving the cutaneous nerve plexus, however, these fine nerve fibres are clearly evident, for the Schwann sheaths and nuclei surrounding both the nerve fibres composing the nerve bundles in the subcutaneous tissues, and the fibres emerging from

Fig. 9 shows several non-medullated nerve fibres which appear to lie within a single stained sheath; the Schwann nuclei can be clearly seen. The fibres depicted lie in skin from an intermediate zone. Methylene blue stained preparation taken from the skin of the leg of a rabbit.

the plexus and passing towards their terminations, are not stained. This absence of medullation in the great majority of nerve fibres composing the

Fig. 10 is from a methylene blue preparation of skin from the leg of a rabbit taken from the centre of the autonomous zone one week after isolated section of the sural nerve. All nerve fibres are seen to be undergoing degenerative changes.

cutaneous nerve plexus has been checked by staining with a modified Spielmeyer-Hortega method (Weddell and Glees, 1941).

Autonomous Zone of the Sural Nerve.—In skin taken from the centre of the area supplied by the sural nerve one week after its section all the nerve fibres are seen to be undergoing degenerative changes (Fig. 10). In skin taken two

weeks after section of the nerve, only a few remnants of degenerating nerve fibres are seen. At longer intervals after nerve section no neural remains of any sort are stained by methylene blue.

In a recent study of the early changes in the degeneration of cutaneous nerve fibres (Weddell and Glees, 1941). it has been shown that degenerative changes can be recognized with methylene blue staining as early as 12 hours after nerve section. " Resistant fibres " (Cajal, 1928), however, may show no change for some days after nerve section. For this reason a minimum period of one week was chosen, in order that no " resistant fibres " should be classed as normal in these experiments.

Intermediate Zones.—In skin which physiologically is classed as an intermediate zone and is adjacent to either the maximal or the autonomous zone of the sural nerve taken one week after operation, both degenerating and normal nerve fibres are seen running side by side in nerve bundles situated beneath the skin (Fig. 11). At the level of the cutaneous nerve plexus, however, all

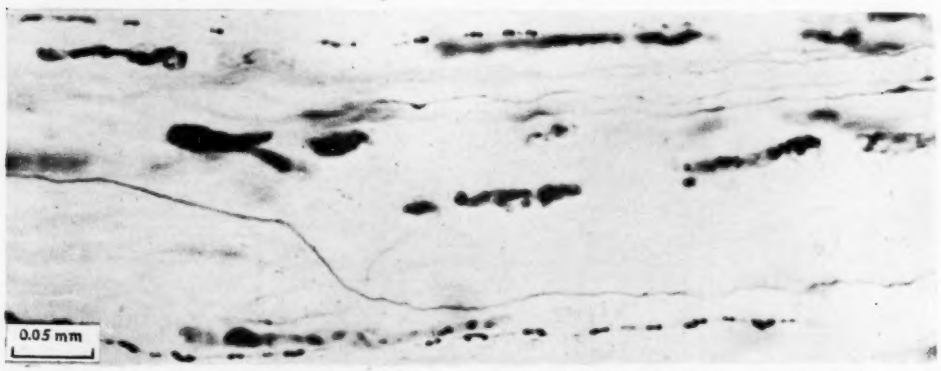

Fig. 11 is from a methylene blue preparation of skin from the leg of a rabbit taken from an intermediate zone one week after isolated section of the sural nerve. Normal and degenerating fibres can be seen lying side by side in a small subcutaneous nerve bundle.

damaged fibres have disappeared, and only those remain which are derived from the intact nerves. The remaining fibres supply hair follicles and give rise to superficially placed nerve nets; the hair follicles, however, are no longer supplied by more than one nerve fibre and the nerve nets are isolated and do not interlock with one another (Fig. 12). The number of nerve fibres in intermediate zones is greatest towards the normal skin and slowly decreases towards the area of sensory loss. The isolated nerve nets invariably extend further towards the denervated areas than the fibres which supply hair follicles. This extension varies in different regions, but reaches a maximum of 2·5 mm. in the areas of the greatest overlap. In such areas the distance between the nets is about half this distance. It is interesting to note here that stimulation of subepithelial nerve nets by needle-pricks in the ear of the rabbit has been proved to evoke nociceptive responses (Woollard *et al.*, 1940).

Growth of Fibres towards the Area of Sensory Loss.—In skin removed at intervals of 2, 3, 4, and 12 weeks following nerve section, and after shrinkage of the area of sensory loss has taken place, it is found that the neurohistological boundary corresponds extremely closely to the boundary obtained physio-

Fig. 12 is from a methylene blue preparation of skin close to the boundary between the maximal zone of the sural nerve and the surrounding denervated skin removed two weeks after section of the tibial and peroneal nerves in a rabbit. It shows the relation between the physiological and neurohistological boundaries. The ink spot represents the physiological boundary, and was tattooed into the skin immediately before staining. Some nerve fibres can be seen extending towards the area of sensory loss. H.F.=Group of hair follicles.

logically and outlined by the tattoo marks. In the majority of cases, the greatest distance between the boundary marked by the tattoo spots and the boundary of the area shown histologically to contain nerve fibres is 2 mm., whilst the average distance is 1 mm. (Fig. 12). Moreover, the neurohistological boundary corresponds within these limits in each case with the ink dots made just before the removal of the skin; ink dots made at previous tests, but which no longer correspond in position to a sensory boundary, are always found to be surrounded by nerve fibres. The great majority of the nerve fibres between the rows of ink spots demarcating the successive boundaries of the areas of sensory loss are non-myelinated; some supply hair follicles, but most of them

Fig. 13 shows the reorientation of nerve fibres which pass towards the area of sensory loss The fibre marked C, which has a growth cone at its termination, is non-medullated and clearly derived from a fibre which proximally terminates around a hair. The fact that the nerve fibres are advancing from the periphery of an intermediate zone is demonstrated by the solitary nerve fibres which innervate the hairs. H.F.=Group of hair follicles. The illustration is from a methylene blue stained preparation taken from the skin of the leg of a rabbit.

are in the form of fine naked nerve fibres, sometimes beaded and arranged in the form of nets, but more often terminating so finely that they can no longer be traced. These fine nerve fibres are always closer to the area of sensory loss than the fibres supplying the hair follicles. The follicles are not innervated by more than one nerve fibre and there is no clear interlock between the nets which are present.

The advancing nerve fibres become reorientated, so that they appear to be growing towards the area of sensory loss (Fig. 13). Histologically it is very difficult to formulate the characteristic features presented by a growing or

regenerating nerve fibre. The majority of nerve fibres which have undergone reorientation end in finely beaded or unbeaded terminals, which get progressively finer, until they can no longer be seen. Growth cones are not commonly present at the termination of these fibres. There are, however, a larger number of such cones present in these areas as compared with those which can be found in normal skin. Growth cones are seen at the end of fibres which come from two different sources. Fibres of one type arise from nerve nets or from fibres innervating hair follicles in intermediate zones and pass directly towards the area of sensory loss (Fig. 14). The more rare type of ingrowing fibre which bears a growth cone can be traced for some distance through the cutaneous nerve plexus and subsidiary nerve bundles of the surrounding normal nerves. Such fibres are more deeply situated and occasionally give rise to branches

Fig. 14 is taken from skin removed 3 weeks after isolated section of the sural nerve. It shows a growth cone surmounting a nerve fibre advancing towards the area of sensory loss from an intermediate zone. The fibre arises from one which itself gives rise to a subcutaneous nerve net. The outline of the sheath into which the fibre is advancing is clearly seen.

which, however, do not proceed to terminal nets or hairs, but either themselves end in growth cones, or become so fine that they pass beyond the limits of visibility (Fig. 15). Ahead of the growth cones there is always seen a faint blue outline of the sheath into which the cones are advancing. The fibres of the first type are only seen extending from intermediate zones. Fibres of the second type are seen at all points around the periphery of the area of sensory loss. In addition, the fibres of the second type are more abundant in the skin taken from the animal 4 weeks after operation as compared with skin taken at shorter intervals following nerve section. This type of fibre is still more abundant in the skin taken from the animal 12 weeks after nerve section; in this case, however, regeneration from the proximal stump had commenced.

Series II. Exposure of the Sciatic Complex without Nerve Section.—In skin removed from the lateral aspect of the ankle of these rabbits one and two weeks

after operation, there are about twice the number of degenerating nerve fibres seen on the operated side as compared with the unoperated side. The individual variations are great, but in every case there are more degenerating nerve fibres

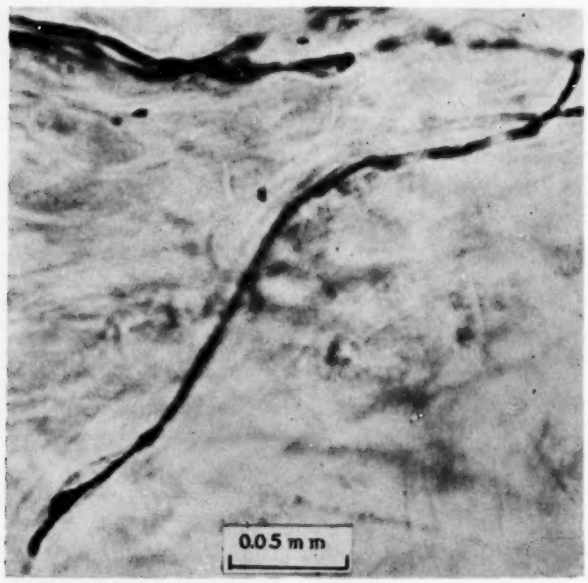

Fig. 15 is from a methylene blue preparation of skin from an area of minimal overlap from the leg of a rabbit removed 4 weeks after isolated section of the sural nerve. It shows a growth cone surmounting a nerve fibre which can be seen entering an empty sheath. The fibre can be traced into a nerve bundle belonging to the adjacent tibial nerve.

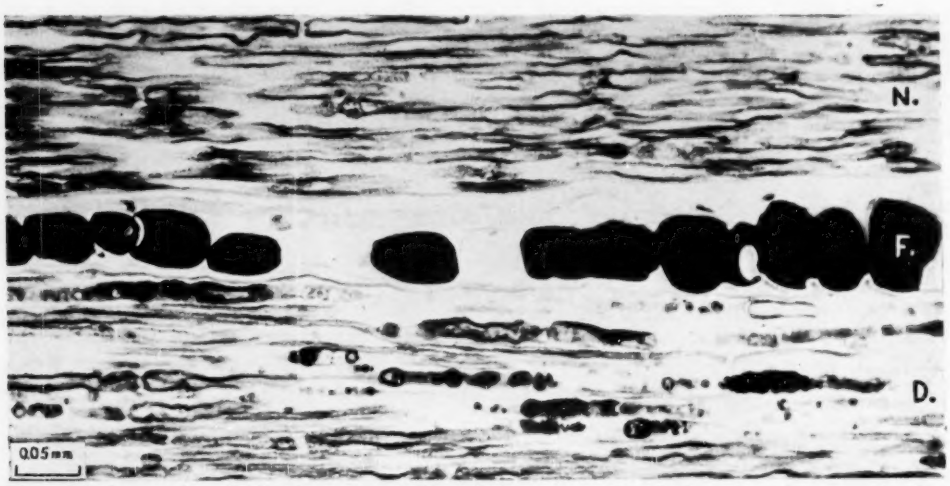

Fig. 16 is from a longitudinal section of the sciatic nerve of a rabbit removed one week after operation. In this case the tibial, peroneal, and sural nerves had merely been dissected free from one another. It shows degenerative changes in one fasciculus only of the sciatic complex. The changes were confined to the nerve below the point of operative interference. Osmic acid stain. N=Normal fibres; D=degenerating fibres; F=fat.

present on the operated side. In the control animal there is no difference between the two sides. In the sciatic nerves there are similarly a larger number of degenerating fibres on the operated side. The degenerating fibres are usually

confined to bundles on one side of the periphery of the sciatic complex, and occasionally a single fasciculus only is affected; moreover, degeneration is only seen in the sciatic nerves below the level of operative interference (Fig. 16). In the control animal no difference can be detected between the sciatic nerves on either side.

Correlation between the Physiological and Histological Observations

The physiological observation that no reactions can be aroused by stimulation within the autonomous zone of the cut sural nerve is paralleled by the histological observation that no nerve fibres extend into such an area. It is also clear that no nerve fibres extend beyond the physiological boundary of the maximal zone of the nerve. There is thus no evidence in the rabbit that after nerve section fibres remain in the apparently denervated area of skin which do not give rise to physiological reactions upon stimulation. It is true, however, that no ink dots were found to be placed at the precise distal extremity of the neural boundary, but always just within it, suggesting that stimulation of a single nerve fibre is insufficient to provoke a withdrawal reaction. Intermediate zones from which fewer, diminished, and often delayed reactions could be obtained possessed a diminished number of nerve fibres which no longer gave rise to endings interdigitating with one another, but on the contrary were clearly separated from each other. The histological findings explain the fewer and diminished physiological reactions which can be aroused, but the cause for the delay is not quite so obvious. It is probably explicable on the basis that a " near miss " of the needle point can occur in an intermediate zone owing to the diminished number of endings present. Such a stimulus may give rise to tissue injury, whose products rapidly spread to nerve terminals which will be stimulated.

The correspondence between the boundary obtained physiologically and that seen histologically proves that an actual extension of nerve fibres towards the area of sensory loss takes place in the absence of regeneration from the proximal stump of the divided nerve. It also becomes clear, after reference to Table 3, that the terms " autonomous," " maximal," and " intermediate " zones have a kinetic as opposed to a static anatomical meaning, for directly after nerve section processes commence which alter the extent of these zones.

Discussion

It is clear from the results recorded above that, after isolated nerve section of the sural nerve, there is a shrinkage in the area of sensory loss due to an ingrowth of nerve fibres from surrounding normal nerves. It is also clear that there is an extension of the maximal zone of the nerve following the section of the tibial and peroneal nerves due to a similar process. This process is a comparatively slow one, as indicated by Table 3, far slower than would be expected in a process of regeneration from the central stump of the interrupted nerve; moreover, it commences before regeneration could possibly have occurred from above. In any case the possibility of regeneration has been

excluded in all but one case.* There is evidence that the source of the fibres passing towards the area of sensory loss is twofold. The majority of the fibres which extend from intermediate zones are non-medullated and spring from nerve fibres which either give rise to nerve nets or supply hairs at the periphery of the area of skin innervated. From other than intermediate zones the number of ingrowing fibres is far smaller, and most of those seen advancing towards the area of sensory loss can only be followed proximally into nerve bundles of the surrounding normal nerves. The latter fibres in all probability arise in two different ways. A minor proportion may come from those fibres which in small numbers are certainly found in process of regeneration in normal nerve trunks (a fact to which attention has been drawn in a recent publication—Weddell and Glees, 1941), and in the later stages others are derived from the regeneration of fibres down the surrounding nerve trunks which (it has been demonstrated in the present investigation) are unavoidably damaged during the course of operation unless the most extreme precautions are taken. In other words, the area of sensory loss may be to a varying degree exaggerated as a result of damage to the surrounding nerves.

The orientation of the advancing nerve fibres and their growth along the sheaths of the nerves which have already degenerated suggest either that they are being attracted towards the area of sensory loss by the sheath itself (or by products of degeneration within the sheath), or that nerve fibres always tend to enlarge their terminal ramifications and therefore make use of the unimpeded pathways offered by the empty sheaths. Either of these suggestions is consistent with the fact that the extension of nerve fibres is virtually confined to intermediate zones where overlapping fibres often run in common sheaths (Weddell and Glees, 1941). In this connection it is noteworthy that with rare exceptions there is never any overlap across the midline of the body, a fact well exemplified following resection of the fifth cranial nerve in man. That the attracting or impelling force is a feeble one is shown by the fact that the fibres advance slowly (Table 3); in addition, no extension takes place from a normal fibre unless it is running in a sheath which is common to a degenerating fibre, that is, in an intermediate zone. Tello (1911) favoured the view that the Schwann cells or their products are responsible for attracting new outgrowths of nerve fibres, whilst Boeke (1936) inclined to the view that the outgrowth of nerve fibres is determined by a neurodynamic principle. It is of interest that Speidel (1933, 1935), working on living nerves in the tail of the tadpole, has also observed an extension of nerve fibres into a denervated area by sprouts from nearby normal nerves.

The area of skin supplied by the sural nerve in the rabbit is very small, and, indeed, the process of extension of in-growing fibres from neighbouring zones may lead to the almost complete disappearance of the area of sensory loss, as in Case 22 (Table 3). In addition, after isolated section of the sural nerve in three very young animals (4 weeks old) it was found that shrinkage of the

* It is interesting to compare the increase in the rate of shrinkage in this case when the onset of the regeneration may be presumed to have commenced, i.e. between the 84th and 91st days.

area of sensory loss was more rapid than in older animals, and the area of analgesia finally disappeared in each case in the absence of regeneration from the proximal stump.

It is interesting to compare the results obtained in such areas with those which are found in man following peripheral nerve interruptions. The observation by Pollock (1920) that there is a shrinkage in the area of sensory loss *before* regeneration from the proximal stump of the interrupted nerve takes place, and particularly that the shrinkage involves the sensation of pain, is exactly paralleled by the present observations. In man, pain is subserved by nerve fibres which terminate in non-myelinated nets, and in the rabbit it is just such fibres which extend furthest towards the area of sensory loss. The advance of fibres which terminate around hairs is probably not paralleled in man for the reason that, unlike those in the rabbit, these fibres are myelinated and the continuity of the sheaths is not apparent in such cases. Rivers and Head (1908) and Stopford (1922) have suggested that in many cases following nerve injury pain recovers before touch or other cutaneous sensations in man. This statement, however, does not appear to be confirmed in every case, and it is suggested that a local advance of non-myelinated fibres, i.e. pain fibres, towards the area of sensory loss which may take place from intermediate zones before regeneration from above commences has been mistaken for regeneration. Pain appears to precede other sensations in recovery when in fact regeneration in the usual sense has not yet commenced.

Both Foerster's (1929) and Guttmann's (1940) observations with regard to the very large degrees of overlap which may appear following peripheral nerve injuries may also be explained in part by this local process of extension. It is noteworthy that the overlap of pain and sweating in these cases is always conspicuous, and both these functions are subserved by non-myelinated fibres.

The very early shrinkage in the area of sensory loss (Case 22, Table 3) cannot be studied histologically owing to the possible presence of " resistant fibres." However, the correspondence between the boundary determined physiologically and that seen histologically is so close two weeks or longer after the operation that the early shrinkage must have some peripheral basis. The presence of an increased number of degenerating nerve fibres in trunks supplying skin bordering the area of sensory loss suggests that, in addition to those fibres which show signs of complete interruption, there are others incapable of transmitting impulses, but which will recover without undergoing Wallerian degeneration. The very rapid recovery in the case of the rabbits of Series II supports this hypothesis. Such findings are paralleled in clinical cases by transient blocks with rapid recovery which follow compression lesions such as " Saturday night " paralysis.

Slight degrees of damage to nerves which supply skin surrounding an area of sensory loss may only be apparent in intermediate zones where the number of fibres is already reduced, but nevertheless they may give a false impression of the actual size of the autonomous zone of the divided nerve. Recovery of such damaged fibres may also lead to the erroneous impression that recovery along the course of the interrupted nerve is commencing. Such slight damage to

nerves which lie in close relationship to an interrupted trunk may be supposed to be common in gun-shot wounds or similar traumatic lesions. It is well known that in such lesions a comparatively trivial superficial wound may be accompanied by more widespread damage in deeply situated tissues. In this connection Foerster (1929) found great differences in the areas of sensory loss between cases in which nerves had been severed cleanly and those which followed gun-shot wounds, the areas in the latter usually being far more extensive than in the former. In fact minimal areas of sensory loss only followed nerve section at aseptic operations; moreover, areas of sensory loss diminished more slowly after gun-shot injuries than after less diffuse lesions. Foerster explained his findings by assuming that the nerve trunks adjacent to the severed nerve were liable to suffer a "concussive" effect, particularly in gun-shot injuries. In view of the observation that the diminution in the area of sensory loss may be due to factors which do not involve regeneration of a divided nerve, it is suggested that in doubtful cases the only certain method of determining whether regeneration is taking place is to block the adjacent nerves with local anæsthetic before carrying out sensory tests.

In view of Foerster's findings, and the fact that in this investigation a small number of degenerating fibres were found in the sciatic nerve following a careful operative procedure which merely involved separating the nerve trunks of the sciatic complex from each other, it is suggested that operative procedures on nerves in man demand the most gentle manipulation.

Summary

1. After section of the sural nerve in the rabbit the outline of the area of analgesia determined by needle-pricks corresponds to the neurohistological boundary almost exactly. Nerve fibres are never seen within the area of analgesia when sufficient time is allowed for all sectioned fibres to degenerate. This area is the so-called autonomous zone of the sural nerve.

2. After section of the tibial and peroneal nerves the outline of the area of remaining sensibility as determined by needle-pricks corresponds with the neurohistological boundary almost exactly. Nerve fibres are never seen within the area of analgesia surrounding this zone when sufficient time is allowed for all sectioned fibres to degenerate. The area of remaining sensibility is the so-called maximal zone of the sural nerve.

3. The difference in the extent of the autonomous and the maximal zones of the sural nerve is the measure of the overlap between this nerve and its surrounding nerves. These areas are the so-called intermediate zones and are characterized by the fact that fewer, diminished, or delayed responses can be aroused from them by needle-pricks. In these areas there is a diminished number of nerve fibres which give rise to endings which no longer interlock with one another, but, on the contrary, are clearly isolated.

4. Following isolated section of the sural nerve there is a shrinkage of the area of sensory loss which commences as early as the day following operation.

There is similarly an extension of the territory innervated by the sural nerve following section of the tibial and peroneal nerves.

5. The correspondence between the boundary obtained physiologically and that seen histologically proves that an actual extension of nerve fibres towards the area of sensory loss takes place. This extension is greatest from the periphery of intermediate zones, and here the advancing fibres are non-medullated. These spring from nerve fibres which give rise to nerve nets or which supply hair follicles at the periphery of the area of innervated skin. Elsewhere the number of ingrowing fibres is smaller and the majority can only be followed proximally into nerve bundles of the surrounding normal nerves; some of these fibres are probably derived from the regeneration of fibres down the surrounding nerve trunks (which it has been demonstrated in the present investigation are invariably damaged in the course of operation, even when most careful precautions are taken).

6. The terms " autonomous," " maximal," and " intermediate " zones have a relative as opposed to a static anatomical significance, for directly after nerve section processes commence which alter the extent of these zones.

7. The physiological and histological findings have been discussed in the light of clinical findings.

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POTASSIUM AND MUSCULAR DISORDERS

BY

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(RECEIVED 18TH NOVEMBER, 1941)

IT has been shown in a previous paper (Cumings, 1939*b*) that the potassium content of muscle was abnormal in two diseases, except for conditions in which fat or fibrous tissue replacement of muscle occurs. Some further muscles from a variety of diseases have since been examined and the results have not given rise to any change of opinion. It has also been shown (Cumings, 1939*b*, 1940) that muscles from myasthenia gravis contain an excess of potassium, which was liberated after prostigmin injection, with a resulting increase of the serum potassium level. There was, however, no increased urinary excretion of potassium, the potassium returning to the muscles as the muscles became weaker.

The amount of potassium present in excess in the serum did not account for all the potassium which was estimated to have been liberated from the muscles. Two more patients with myasthenia have been investigated to confirm the previous results and to determine whether the red cells also showed an increase in their potassium content, and the results are recorded. Some experimental results are also recorded in which rabbits were injected with substances extracted from gelsemium roots in an endeavour to produce muscular disorders in any way comparable to myasthenia.

Potassium Content of Muscles in Various Conditions

The potassium content of muscles taken at biopsy from a variety of diseases was estimated as previously described (Cumings, 1939*a*), and the results are seen in Table 1, together with the effect prostigmin (mgm. i) had upon the potassium content of the muscle in some of the disorders.

It is seen that in the majority of diseases there is no abnormality in potassium content. The potassium contents found in muscles with fat replacement, such as in the patient with myopathy, and in muscle in the case of myotonia are in accord with previous findings. The patient with familial periodic paralysis showed a normal potassium content during the non-paralytic stage. It was, unfortunately, not possible to obtain muscle during an attack of weakness.

* A grant was received from the research funds of the National Hospital towards part of the expenses.

TABLE 1.—POTASSIUM IN MUSCLES IN DISEASE

NAME	DISEASE	POTASSIUM IN GRAMMES PER CENT. OF DRY WEIGHT	
		BEFORE PROSTIGMIN	AFTER PROSTIGMIN
F. S. ..	Myopathy with marked fibrosis	0·23 0·19	—
T. ..	Tetanus	1·18	—
C. ..	Hyperthyroid	1·44	1·12
B. ..	Myxœdema	0·63	1·4
C. ..	Myotonia	0·54	—
W. ..	Late myopathy	1·26	—
K. ..	Familial periodic paralysis—non-paralytic stage	0·82	—
R. ..	Parathyroid tumour—		
	Before operation	0·40	0·193
	After operation	1·3	1·6

The patient with a parathyroid tumour gave a very interesting result and is the only example of variation from the previous findings. The patient came to hospital complaining of muscular weakness, but she was found to have a parathyroid tumour, which was successfully removed. Subsequently her weakness slowly disappeared. Muscle taken prior to operation showed a low potassium, with a diminution of potassium after prostigmin, but when the patient was well, both resting muscle and muscle after prostigmin showed normal potassium levels. It would appear that the muscular weakness was associated with a low potassium level in the muscles. The phosphate level was raised to 1·94 per cent. by dry weight. It is not possible on this single example to offer any explanation, and it is the one variation found in this series from those previously recorded.

Myasthenia and Potassium

Two patients with severe myasthenia were examined in a manner previously described (Cumings, 1940), with, however, a few variations. The diet—a war-time one—was somewhat more liberal in its content of potassium and was well tolerated, except that one patient vomited once, necessitating an estimation of potassium in the vomit. The patients as a result were in positive potassium balance. The potassium content of the whole blood as well as that of the serum was estimated. Potassium was added to the diet for the latter part of the experiment in the same dosage and in the same manner as previously, and prostigmin injections (mgm. i) were given on two occasions to each patient. The time relationship of these procedures can be seen from Figs. 1 and 2 on which the urinary excretions of potassium are recorded.

Results

The effect of the prostigmin injections on the serum and whole blood potassiums are given in Table 2.

TABLE 2.—POTASSIUM AND INORGANIC PHOSPHATE IN BLOOD BEFORE AND AFTER PROSTIGMIN

	MR. S.				MRS. T.			
	SERUM		WHOLE BLOOD		SERUM		WHOLE BLOOD	
	POTASSIUM	INORGANIC PHOSPHATE	POTASSIUM	INORGANIC PHOSPHATE	POTASSIUM	INORGANIC PHOSPHATE	POTASSIUM	INORGANIC PHOSPHATE
Before first prostigmin injection	17·6	3·5	104·6	18·4	16·9	2·1	112·6	10·0
¾ hour after first prostigmin injection.. ..	20·2	3·5	110·0	17·6	18·1	2·5	145·0	14·0
Before second prostigmin injection	26·0	4·0	164·4	27·2	28·6	3·8	175·5	16·4
¾ hour after second prostigmin injection ..	30·1	4·1	209·4	19·2	34·2	3·4	192·5	16·4

All results in milligrams per cent.
Serum sodium figures showed no variation between each pair of results.

The effect of prostigmin was similar clinically and biochemically to that found before, and in addition there is an increase of potassium in the red cells. The increase of potassium in the serum is not quite so marked as was seen previously, and may have been due to two factors. One reason was that both patients were in a positive potassium balance, and the other because neither of these patients was so severely affected with the disease as were the two previous patients.

The daily intake of potassium is recorded in Table 3. The first of the two patients received exactly the same foods and the same quantity of them each day, and it was this patient who vomited once.

TABLE 3.—INTAKE OF POTASSIUM

DAY OF EXPERIMENT	MR. S.		MRS. T.	
	DIET	MEDICINE	DIET	MEDICINE
1	1·254 gm. of K.		1·426 gm. of K.	
2	1·254 ,,		1·368 ,,	
3	1·254 ,,	3 gm. of K.	1·691 ,,	
4	1·254 ,,	3 ,,	1·286 ,,	3 gm. of K.
5	1·254 ,,	3 ,,	1·947 ,,	3 ,,
6	1·254 ,,	3 ,,	1·526 ,,	3 ,,
7	1·254 ,,	3 ,,	1·567 ,,	3 ,,
8	1·254 ,,	3 ,,	1·254 ,,	3 ,,
9			1·332 ,,	3 ,,
10			1·059 ,,	3 ,,
TOTAL ..	10·032 gm. of K.	18·0 gm. of K.	14·456 gm. of K.	21·0 gm. of K.

The potassium balance of both patients is given in Table 4, which shows the total intake and total excretion of potassium.

TABLE 4.—POTASSIUM BALANCE

	MR. S.	MRS. T.
K intake in food	10·032 gm.	14·456 gm.
K intake in medicine	18·0 ,,	21·0 ,,
Total K intake	28·032 ,,	35·456 ,,
K output in urine	15·023 ,,	27·347 ,,
K output in fæces	3·060 ,,	1·736 ,,
K output in vomit	0·079 ,,	
Total K output	18·162 ,,	29·083 ,,
BALANCE	+9·87 gm. for 8 days. +1·23 gm. per day.	+6·373 gm. for 10 days. +0·637 gm. per day.

Whereas both patients previously examined were in negative balance, these two were definitely in positive balance.

The urinary excretion is set out in Figs. 1 and 2, together with the times of the prostigmin injections, and the days on which additional potassium was administered.

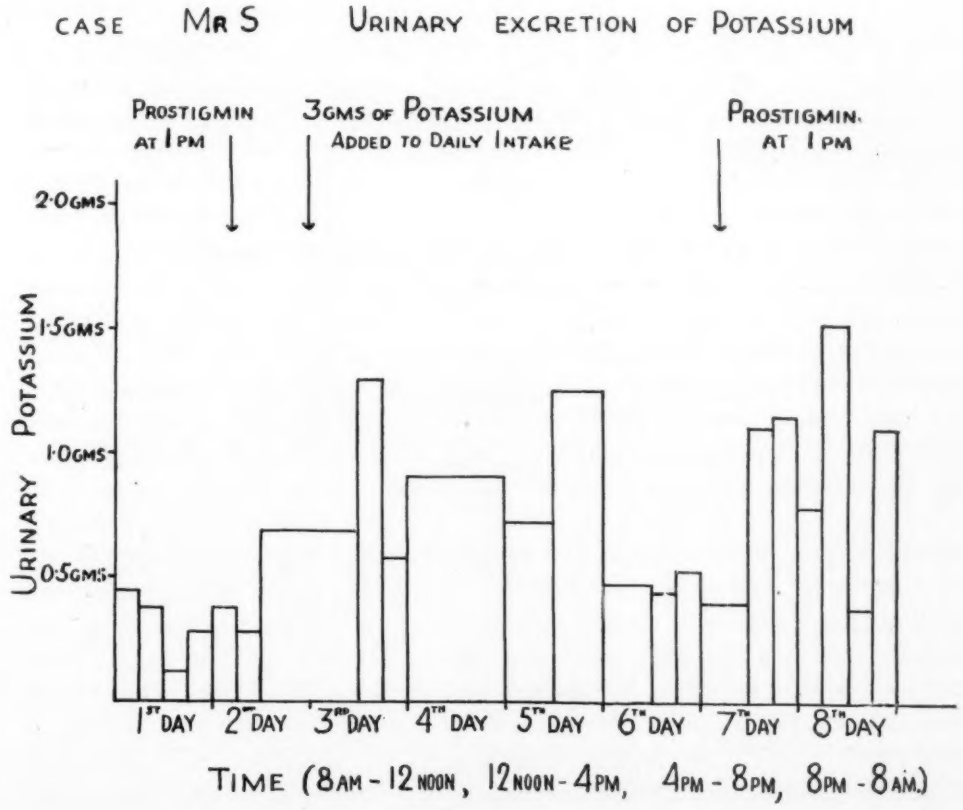

Fig. 1.

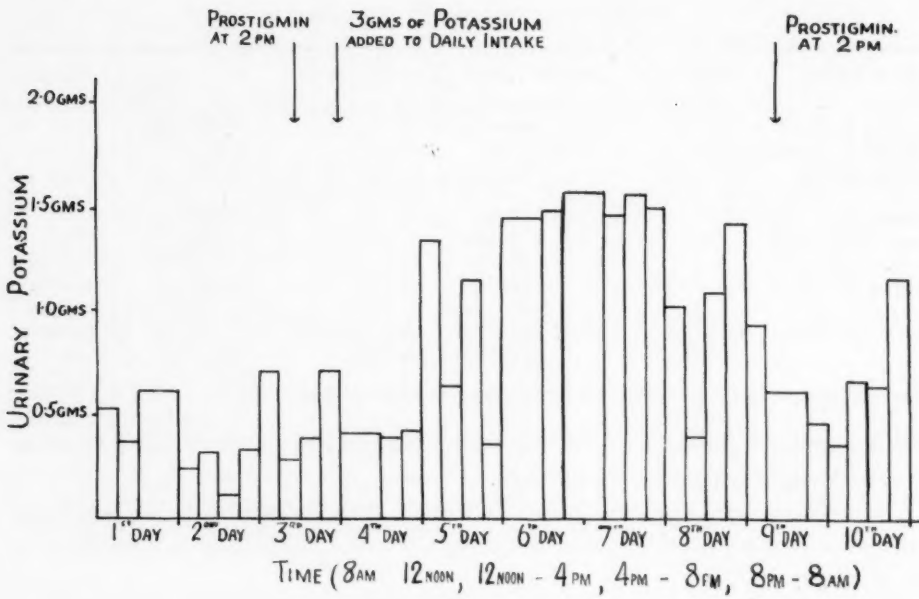

Fig. 2.

It is seen that there was no increased urinary excretion of potassium as a result of the prostigmin, and that this is in accord with the previous experiments.

Fæcal excretion is given in Table 5 and shows no increase of potassium following prostigmin.

TABLE 5.—EXCRETION OF POTASSIUM IN STOOLS

DAY OF EXPERIMENT	MR. S.		MRS. T.	
	WEIGHT OF STOOLS, DRIED	TOTAL AMOUNT OF K PRESENT	WEIGHT OF STOOLS, DRIED	TOTAL AMOUNT OF K PRESENT
	GRAMMES	GRAMMES	GRAMMES	GRAMMES
1	—	—	—	—
2	32·0	1·216	7·8	0·110
3	—	—	14·9	0·249
4	5·9	0·173	16·65	0·082
5	5·7	0·62	2·7	0·010
6	—	—	26·35	0·208
7	—	—	12·6	0·32
8	—	—	16·2	0·078
9	16·8	0·706	—	—
10	12·5	0·345	12·5	0·192
11	—	—	17·5	0·478

Discussion

It is seen that the results obtained in these investigations on the two patients on a positive potassium balance, although conducted under some difficulties, owing in part to food rationing, were in agreement with those of previous experiments. It is also seen that the red blood cells show some increase of potassium content after prostigmin injections, and that the increase in whole blood potassium more nearly approximates to the amount of potassium liberated from affected muscles, whereas in the previous experiments the increased amount found in the serum was not sufficient to account for the total amount of potassium that one would expect to have been set free from the affected muscles. However, one would not expect to find a large amount of potassium being taken up by the red cells, as it has been shown by Hahn, Hevesy, and Rebbe (1939) in their experiments conducted with ^{42}K—a radioactive isotrope of potassium—that the red cells only took up a relatively small amount of potassium, whereas muscle was able to take up nearly three times this amount of ^{42}K. Davson and Danielli (1938) showed that normal red cells prior to hæmolysis liberated little potassium, so that one would expect that the bulk of the potassium liberated from the muscles would be found in the plasma if it is to be returned again to the muscles. It is seen that there is no increase of urinary potassium after the prostigmin injections, and this is in accord with the previous results.

It had been suggested that a lack of nerve impulses to the muscles might result in an increase of muscle potassium. It was possible to show that this is not so both in human muscle and also experimentally in animals. One patient who had a spinal anæsthetic for a lower limb amputation had four samples of muscle removed after thirty minutes complete paralysis. None of the muscles showed a raised potassium content. Another patient who had a completely paralysed muscle after a severance of the motor nerve had a biopsy two months after the injury, and the muscle contained a normal amount of potassium. These results are recorded in Table 6, together with the results obtained from the animal experiments. Rabbits under nembutal anæsthesia were used for these experiments and samples of muscle were taken at varying intervals up to $2\frac{3}{4}$ hours after the nerve supplying the muscle had been cut. Another rabbit had a tourniquet applied to the hind leg, completely obstructing the arterial supply, but the potassium content was very similar before and $1\frac{1}{2}$ hours after this procedure.

The results obtained in these and preceding experiments all suggest an error in the potassium content of muscle primarily associated with myasthenia but not necessarily causing it. It is of interest here to note that Needham *et al.* (1941) have recently conducted some very interesting and instructive experiments. They have approached the subject of muscular activity and its relationship to potassium from a different aspect, using myosin birefringence and the action potassium and adenylpyrophosphate has upon it. They state that from previous work it would appear that adenylpyrophosphatase is either myosin or a related protein, and that muscular contraction is essentially a

molecular contractility of protein chains. Their own experiments indicate that adenylpyrophosphate has a direct influence on the shape of the myosin particles. Further, they found that a certain amount of potassium in contact with myosin caused a decrease of flow birefringence, i.e. a decrease in asymetry of the molecule and so a shortening of the particles and possibly a diminution in size also. However, when the amount of potassium was further increased the flow birefringence returned somewhat. There would thus appear to be a definite relationship between the amount of potassium present and the particle size of the myosin, but these results only relate to in vitro experiments, and may not be absolutely comparable to the conditions occurring in the actual muscle fibrils. v. Muralt (1932) has also shown that during a single isometric twitch the birefringence decreases and returns to normal by the end of relaxation. Whether this is associated with a variation in muscle potassium at the same time is not known. Fenn and Cobb (1936) in animals obtained a loss of potassium from muscles during exercise, and Keys (1940) showed an increase in plasma potassium after short exercise, although in these experiments the red cell potassium decreased. Cumings and Maas (1939) found no such alterations in serum potassium in normal human subjects, although in myotonia there was a decrease of serum potassium following exercise. It is possible that it is the relationship the muscle potassium bears to the potassium in the surrounding fluid that is the important factor, and if this is so it might explain the beneficial clinical results Laurènt and Walther (1935) obtained in myasthenia with large doses of potassium by mouth, with subsequent increase of serum potassium. It does seem possible that the work of Needham as applied to myasthenia might yield valuable results. However, there is no evidence to show whether there is an error in the nature of the myosin or of the metabolism of potassium and its relationship to myosin, or whether some other factors controlling potassium metabolism are concerned.

TABLE 6.—EFFECT OF NERVE SECTION ON POTASSIUM CONTENT OF MUSCLE

Case 1	Four samples of muscle removed 30 minutes after spinal anæsthetic.						
	K gm. per cent. by wet weight ..	0·2	0·27	0·26	0·31		
	K gm. per cent. by dry weight ..	0·7	0·92	0·9	1·05		
Case 2	Muscle 2 months after complete nerve section.						
	K gm. per cent. by wet weight ..	0·31					
	K gm. per cent. by dry weight ..	0·93					
		Time, after nerve section					
		Before nerve section	½ min.	5 mins.	30 mins.	60 mins.	90 mins.	165 mins.
Rabbit 1	K gm. per cent.	0·9	1·0		0·8		0·7	
„ 2	dry	1·5		1·5		1·7		1·4
„ 2 .. .. (opposite side)	weight	1·5					1·7 after complete arterial obstruction.	

Marenzi (1938), from his experiments with cortico-suprarenal hormone, suggested that this substance regulates the fixation of potassium in the liver and the heart, but not in muscle, and also that it controls the renal excretion of potassium, as he found that although there was an increase of serum potassium after administration of this substance following suprarenal removal in animals, there was no increase of urinary excretion of potassium. Ferrebee *et al.* (1941) found that the administration of desoxycorticosterone acetate to dogs produced muscular weakness, with a loss of muscle potassium, but that there was also an increased urinary excretion of potassium.

Experiments with Gelsemium

It was thought possible to find a drug that would produce muscular weakness in animals and that this would perhaps enable one to investigate the relationship of potassium to muscular activity more easily. Gelsemium was chosen as being likely to give rise to such conditions, as Chou, in a series of papers (1931*a*, *b*, *c*) had succeeded in producing in rabbits some degree of muscular weakness. Chou had used both the American yellow jasmine and later a Chinese variety, Kou-Wen (*Gelsemium Elegans* Bth.). Both these plants were obtained, and the technique used by Chou followed as closely as his descriptions allowed, using the rhizome and roots ground to a powder before extracting with alcohol and with acid. Rabbits were then tested with varying doses of all extracts obtained, but in no case was there any muscular weakness, nor did the rabbits appear in any way affected. The serum potassium was estimated before and after the intravenous injections and no change took place, e.g. one rabbit had serum potassiums of 27·8 mgm. per cent. before and 24·9 mgm. per cent. three hours after the injection. One rabbit was given Kou-Wen to eat in 100 gm. doses a day, and although it has been said that parts of the plants are fatal to man if eaten, this animal showed no abnormalities. It has not therefore been possible to produce muscular weakness in animals using gelsemium root.

Summary

The potassium content of muscle in a variety of diseases has been estimated.

Potassium balance experiments on two patients with myasthenia gravis were conducted. Red blood cells as well as serum showed an increased potassium content after prostigmin injections, but no increased urinary excretion took place. These results are discussed in the light of recent physico-chemical work.

Division of the motor nerves to muscles does not affect their potassium content.

Substances extracted from the roots of American and Chinese varieties of the yellow jasmine produced no muscular disorders in rabbits.

My thanks are due to Dr. Grainger Stewart and Dr. J. Purdon Martin for allowing me access to their patients, to Mr. Harvey Jackson, F.R.C.S., and Mr. A. J. Cokkinis, F.R.C.S., for their help; and to Messrs. British Drug Houses for so kindly obtaining for me supplies of the gelsemium roots.

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THE EFFECT OF PROSTIGMIN ON THE URINARY EXCRETION OF POTASSIUM IN THE NORMAL SUBJECT

BY

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(RECEIVED 18TH NOVEMBER, 1941)

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PREVIOUS work (Cumings, 1940) on the effect of prostigmin (mgm. i) in patients suffering from myasthenia gravis showed that although potassium was liberated from affected muscles and circulated in the blood, the urine did not show any increased amount of potassium. It was assumed that prostigmin did not in any way cause this retention of potassium in that it had no effect on the kidney, and upon this assumption certain deductions were made. The present paper describes an attempt to show that this assumption was correct.

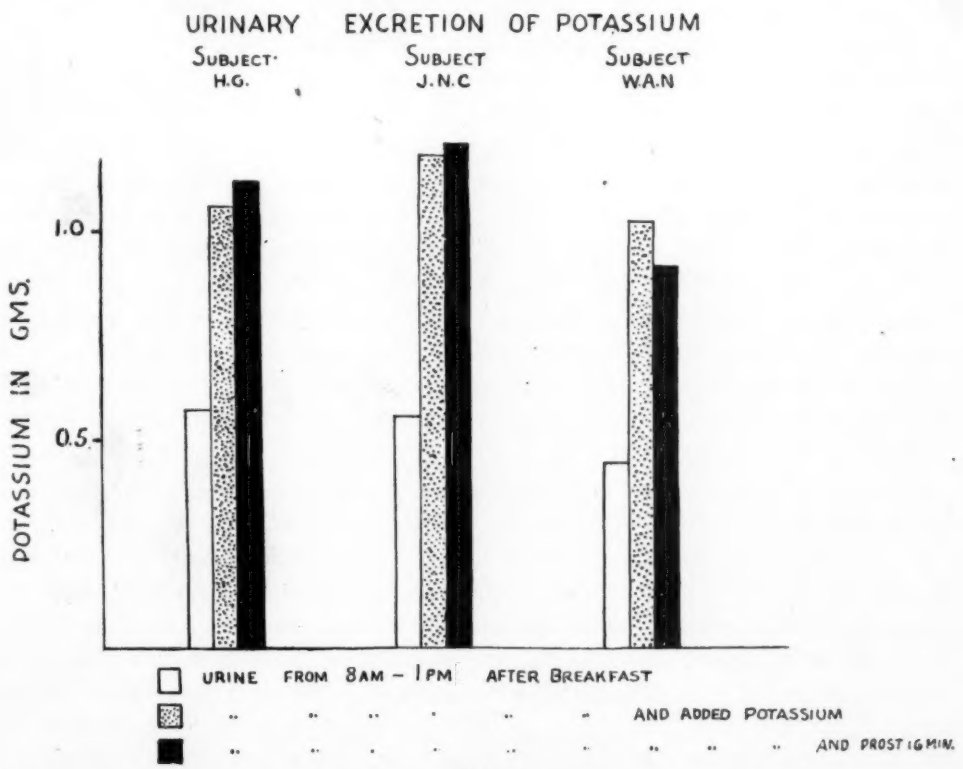

Fig. 1.

The urinary excretion of potassium was studied in three normal subjects. All urine passed between 8 a.m. and 1 p.m. was collected, breakfast having been taken before 8 a.m. after the bladder had been completely emptied. No food was taken during the experimental periods and a similar breakfast was taken on each day. Three test periods were conducted, and in the first urine was collected after breakfast only, during the second period 1 gm. of potassium as dipotassium hydrogen phosphate was taken immediately after breakfast and the specimens of urine again collected. Finally the urines were collected as in the second period, but with prostigmin injections immediately after the added potassium had been given. Urine was also collected from 1 p.m. to 5 p.m., but as most of the added potassium was excreted during the morning, the results of these examinations are not recorded.

Fig. 1 shows the results obtained, from which it is seen that prostigmin has had no effect on the excretion of potassium, as the amount of potassium excreted after the prostigmin injections is slightly higher in two of the subjects and only slightly lower in one subject, who it is seen also excreted less potassium than either of the other two. It is evident, therefore, that the previous assumption was correct, and that prostigmin was not the direct cause of the retention of potassium in the patients with myasthenia.

* An expenses grant was received from the National Hospital Research Fund for which my thanks are due.

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TRAUMATIC SUBDURAL EFFUSIONS

BY

A. A. McCONNELL

(RECEIVED 20TH NOVEMBER, 1941)

PENFIELD (1924) first used the term " effusion " applied to fluid in the subdural space, and Naffziger (1924) was the first to draw attention to subdural accumulations of fluid in acute head injuries. In an earlier paper the former (Penfield, 1923) had demonstrated that the amount of fluid in the space varied from a few drops to 1 c.cm. in a dog of 5 kilogrammes. There is no publication dealing with the normal amount of subdural fluid in the human being or with its constitution. Observations at operation on non-traumatic cases suggest that the amount of fluid normally present is not sufficient to envelop the cerebral hemispheres; the operative field is usually the highest area of the skull, and when the dura is opened there is no obvious collection of subdural fluid and no overflow. When, however, the dura at the base of the brain is opened with the patient's head erect, as in the temporal approach to the gasserian ganglion, a considerable amount of fluid can be obtained without incising the arachnoid membrane. It would seem that the fluid indigenous to the subdural space is free and tends to accumulate in the dependent parts of that space. Subdural fluid may be deemed to be in excess: (*a*) when it spurts or flows through an opening in the dura at the highest part of the skull; (*b*) when the escape of fluid leaves the brain obviously depressed; or (*c*) when the escape of fluid is followed by free pulsation of a brain in which pulsation has been absent. Sometimes the brain engages in the dural opening and does not pulsate, thus giving the impression of cerebral œdema, but the passage of a spatula under the dural edge releases fluid and the brain falls away and begins to pulsate freely. When there is a bilateral excess of fluid there does not appear to be any communication between the two sides; each demands a separate opening. Occasionally a definite excess of fluid may be found over one part of a hemisphere and none over another part of the same hemisphere. The term " subdural hydroma " has been given to these apparently encysted collections of subdural fluid.

It is easier to demonstrate an excess of subdural fluid in the living than in the dead subject, for unless a premeditated search be made for it at autopsy, the fluid may escape during the examination, and, unlike blood, leave no trace of its former presence; the pathologist merely remarks, " A lot of fluid seems to be present."

Excessive amounts of fluid have been found in the subdural space soon or some time after a head injury in 30 cases. These cases fall into four groups.

Group 1.—Patients whose condition was deteriorating, usually within 48 hours of the accident (8 cases).

Group 2.—Patients who were in the process of recovery from definite general cerebral contusion, but in whom full recovery seemed to have been checked.

Group 3.—Patients suffering from headache, dizziness, and vague symptoms of nervous instability dating from a head injury.

Group 4.—Patients in whom headache and occasionally some definite nervous system, constant for the individual, started some time after a head injury.

Case reports illustrative of each of these types will be given.

GROUP 1.—*Patients whose condition was deteriorating, usually within* 48 *hours of the accident* (8 *cases*).

Case 1.—A. N., male, aged 30, was arrested after a street fight, and spent the night in prison. Next morning he was found to be drowsy, slow in answering, and the pulse rate was 50. There was a small scalp wound on the right side. No focal signs could be found. On the diagnosis of extradural hæmorrhage an opening was made in the right temporal region. There was no blood outside the dura, but when the latter was opened a large quantity of clear fluid under great tension rushed out, leaving the brain depressed for more than a centimetre. The patient made a rapid and complete recovery. He remembered every detail of the fight and the blow on the head.

Case 2.—M. E., female, aged 14 months. Admitted 20th September, 1934.

Two days before admission the baby, when trying to walk, fell. The parents did not think that she was hurt as she immediately resumed her attempts to walk. Next day the movements of the left hand appeared weak, and the day after both left arm and leg were paretic. She became quiet and listless and did not cry. On admission she noticed what was going on about her. The left limbs were flaccid and showed no spontaneous movement; Babinski reflex positive on the left; the left side of the face was weak.

An opening was made above the right temporal region. When the dura was opened a large amount of clear fluid escaped and the brain expanded. 22nd September. Some spontaneous movement of the limbs, later, recovery. 3rd October. Discharged.

These two cases may be regarded as examples of pure expanding lesions, as there was no evidence of initial concussion. In the next six cases the subdural fluid was associated with general cerebral contusion.

Case 3.—K. J., male, aged 58, slipped in the street and fell on the back of his head on 19th July, 1940. He was dazed and the police brought him to a Dublin hospital at 12.30 p.m. A small scalp wound in the occipital region was dressed. There were no indications of intracranial injury, but the patient was kept in for the night and discharged next morning apparently well.

Next day at 5 p.m., after a " lucid interval " of 29 hours, he suddenly became unconscious, was taken back to hospital and later transferred to the Richmond Hospital. On examination. Comatose, did not react to painful stimuli. Pupils equal and reacted to light. The right side of the mouth seemed to sag. There was tone in all limbs and there was no Babinski reflex. Blood pressure 120/60; pulse 88; respirations 36; temperature 99·8° F. Fifteen ounces of urine were withdrawn by catheter, sp. gr. 1010, no abnormal constituents. Blood urea 91 mgm. per 100 c.cm.

An opening was made in the left temporal region. When the dura was nicked a jet of fluid shot up several inches; complete opening allowed a large quantity of

fluid to pour out. The brain was not pulsating and it remained about 1 cm. deep to the dura. A spatula passed into the subdural space gave the impression that the hemisphere was too small for the skull. An area of hæmorrhage about 1 cm. in diameter was noted on the surface of the temporal lobe.

A similar opening was made in the right temporal region and the dura opened. There was no subdural fluid but the brain was retracted about 1 cm. It appeared normal but did not pulsate. These operations did not influence the patient's condition in the slightest. 22nd July. Generalized fits, controlled by 1 c.cm. luminal. Lumbar puncture, normal fluid and normal pressure. Blood pressure 160/90. He died next day.

Post-mortem examination revealed gross general arteriosclerosis, the basilar, carotid, and coronary arteries being veritable " pipe-stems." The brain did not appear as retracted in death as in life and no lesion was found, apart from the arteriosclerosis.

Case 4.—C. J., aged 42, was admitted to a Dublin hospital shortly after a motor accident on 22nd July, 1939. He walked into hospital; he spoke sensibly, but seemed rather dazed. A scalp wound in the left occipital region was stitched. Next day. He was still rather dazed and talked erratically, but physical examination was negative and he was allowed to go home.

25th July. Re-admitted. He could speak, and understand what was said to him, making slow but intelligent answers. The left side of the face and the left arm were paretic; the left leg was weaker than the right and there was a positive Babinski on the left side. Pulse 86. A diagnosis of epidural or subdural hæmorrhage was made.

Operation. Local anæsthetic. When the needle was inserted he became very excited and had to be held on the table. An opening was made in the right temporal region, exposing a normal dura, which, however, did not pulsate. When the dura was opened there was a gush of slightly blood-stained fluid with a few small clots. A large quantity of fluid escaped. The brain appeared normal. It began to pulsate, but it remained two centimetres below the level of the dura. The intention had been to open both sides of the head, but the patient's excitement had not abated, and it was argued that the operative findings explained the symptoms. The wound was drained with rubber tissue.

26th July. More difficulty in answering questions. Very restless.

27th July. More drowsy. Complete left hemiplegia. The wound was re-opened, but no fluid was obtained; the rubber tissue was removed. An opening in the left temporal region was made, and exactly the same condition found as at the first operation—a rush, then a copious outflow, of slightly blood-stained fluid. After a transitory improvement the patient became worse; first delirious, then deeply comatose. Drainage ceased, and the rubber tissue was removed. Within the next four days the wounds were re-opened twice and quantities of clear fluid escaped. After that no more fluid was obtained, but the brain was shrunken. Intravenous injections of glucose were given.

A week after the second operation the patient began to react and was able to drink, but he did not become conscious of his surroundings till the seventeenth day, when he began to move his left arm. From this date recovery was uneventful. There was complete amnesia for the accident and most of his stay in hospital.

On 17th March, 1940, his wife reported that he had had a fit, in which his left side " worked." Two days later examination showed a slight relative weakness of the left arm and left leg. The patient said that he felt weak and nervous but was otherwise well.

Case 5.—F. M., male, aged 26, admitted 30th August, 1937.

At 11 p.m. on 29th August the patient collided with another cyclist and was

thrown to the ground. He was brought unconscious to a County hospital. Pulse 83; temperature 97° F.; pupils equal and reacting; scalp wound 3 in. long in left frontal region. Next morning he could be partially roused by painful stimulation. Pulse 68 to 52. Next day at 11 p.m. he was very drowsy, but could be wakened and induced to answer questions. Pulse 48. Pupils dilated, equal, and reacted to light. There was relative weakness of the right side of the mouth, the right arm, and the right leg. There was a Babinski sign on the right foot.

Operation. Local anæsthetic. The scalp wound was excised and closed. An opening was made in the left temporal region. The dura was tense and not pulsating. When it was incised there was a rush of clear fluid under tension. A large amount escaped, and the brain was then seen to pulsate normally and rise to dural level. Pulse rate was now 70.

Recovery was uneventful and complete.

Case 6.—O'T. P., aged 48, admitted 8th August, 1940.

Ten days before admission he fell off a horse and was immediately unconscious. There was some bleeding from the ears and nose at the time. The right pupil was dilated, but reacted to light, and he had a grasp reflex in both hands. Lumbar puncture, pressure 100 mm., fluid blood-stained.

8th August, 4.30 p.m. Semi-comatose, reacted slightly to painful stimuli. Pulse 100; temperature 98·8° F., moving arms and legs; grasp reflex both hands. Lumbar puncture. Fluid did not rise in manometer; yellow tint; protein 0·04 per cent., cells 4 per mm. 3 c.cm. removed. Blood pressure 120/80. At 9 p.m. on supraorbital pressure the right side of the face alone reacted. The right hand grasped the sheet firmly; the left was passive.

Next day he was deeply unconscious. Pulse 140; temperature 102° F.; respirations 60. Pupils moderate and equal, but the left did not react to light. Some tone in right arm; none in left. Blood pressure 90/75.

A drill hole was made in the right temporal region. A nick in the dura released fluid under tension. A needle was passed through the opening and 30 c.cm. of dark yellow fluid was aspirated. The opening was enlarged and considerably more fluid escaped. The brain, which did not pulsate, lay 1½ centimetres from the dural level. The protein content of the fluid was 0·18 per cent. A similar opening was made on the left side. A smaller amount of fluid was obtained and the brain was retracted about ½ centimetre. Blood pressure remained at 90/75.

The operation did no good, and the patient died 4 hours later.

Post mortem. A considerable amount of fluid under scalp in region of right opening. Posterior fossa normal; no blood or excess of fluid. Dura slack; brain shrunken. When the brain was removed this shrinkage could not be appreciated, nor could the amount of fluid still present be estimated. On the lateral posterior aspect of the right orbital surface there was a linear laceration about 3 mm. deep. On the lateral surface of the right temporal lobe, just behind the tip of the temporal pole, was an area 2 cm. in diameter of subarachnoid hæmorrhage overlying a shallow laceration.

In the first two cases there was no evidence of cerebral injury, and it would appear that subdural fluid accumulated rapidly and produced the deterioration in consciousness and the focal signs in the same manner as these phenomena are produced by a progressive hæmorrhage. In the next six cases cerebral damage was immediate, and later subdural fluid accumulated sufficiently to modify the clinical picture. The fatality in Case 3 may be attributed to compression by the fluid, though the role of the arteriosclerosis must be considered; in the other fatal cases cerebral damage was probably more responsible.

These cases were in most respects similar to those of intracranial hæmorrhage, and it does not seem possible to make a differential diagnosis. Hæmorrhage and accumulations of subdural fluid may be classified together as " traumatic expanding lesions."

The eight cases of Group I are summarized below.

TABLE 1.—*Group I.* SUBDURAL FLUID ACTING AS AN EXPANDING LESION

COURSE OF CONSCIOUSNESS	ONSET OF FOCAL SIGNS	PULSE-RATE	RESULT
1. Became drowsy 12 hours after injury	None.	50	Recovered.
2. Listless 24 hours after injury	Hemiparesis 48 hours.	110	Recovered.
3. Concussion; lucid interval of 29 hours. Coma ..	Facial weakness 29 hours.	88	Died.
4. Concussion to automatism	Hemiparesis 4 days.	86	Recovered.
5. Concussion to accessibility	Hemiparesis 24 hours.	68 to 48	Recovered.
6. Concussion to semicoma ..	Babinski and facial weakness immediate. Hemiparesis 48 hours.	100 to 140	Died.
7. Concussion to semicoma ..	Hemiplegia 11 days.	100	Died.
8. Comatose since injury ..	Bilateral rigidity. Babinski 27 hours.	100	Died.

GROUP 2.—*Patients who were in the process of recovery from definite general cerebral contusion, but in whom full recovery seemed to have been checked.*

Case 7.—S. P., male, aged 22, admitted 22nd January, 1930. Referred by Mr. J. F. O'Connor, F.R.C.S.I., Limerick.

20th November, 1929. The patient fell off the back of a motor car. His head hit the ground and he became unconscious immediately. He was brought to the County hospital, where he remained stuporous for ten days, but another fortnight passed before he was able to answer simple questions intelligently. He remained mentally confused and irritable. No neurological signs were discovered. The pulse rate hovered between 40 and 50 for three weeks. As the mental state was getting worse he was transferred to the Richmond Hospital.

22nd January, 1930. The patient was very excitable and said that he never felt better in his life. He did not understand why he had been sent to Dublin and he demanded immediate discharge. There was great difficulty in controlling him, in spite of bromides and hyoscine. He talked freely, but it was obvious that his memory for recent events was defective and that his talk had little relation to reality. Pulse rate 80 to 100.

The then neurologist and the psychiatrist agreed that the case was one of dementia and that it was doubtful if the injury had much to do with the mental condition. They advised immediate certification and removal to an asylum.

Radiographic examination, however, had revealed a stellate fracture of the right parietal bone, with a fissure traversing the line of the middle meningeal artery, and the right pupil, though reacting, was larger than the left. It was therefore decided to do an exploratory operation before certification. 25th January. General anæsthesia. An opening was made in the right temporal region. There was no epidural hæmorrhage. When the dura was opened a considerable amount of blood-stained fluid escaped. The brain lay well below dural level and did not expand. There was some excess of subarachnoid fluid, which gave the brain a watery appearance. He at once became amenable and more rational.

On the fourth postoperative day he could remember events up to the accident,

understood where he was and why. Felt well. From this date recovery was uninterrupted and the patient was discharged on 5th February. Mr. O'Connor wrote in July 1941 that the patient had remained well and seemed quite normal.

Case 8.—Y. T., male, aged 40, admitted to Richmond Hospital, Dublin, 10th August, 1940.

On 2nd August he fell, the back of his head hit the ground, and he became comatose immediately. After admission to a local hospital he passed into delirium, which continued for seven days.

10th August. Examination: the patient was quiet; he would not answer questions, but talked incessantly and incoherently. Pulse 50; blood pressure 150/80; no neurological signs. 13th August. Still mentally confused, repeating phrases over and over again. Answered the same questions differently each time. Inclined to make jokes. When asked "Where are you?" he answered, "I'm here." "What age are you?" "I'm old enough to know better." He could go to the lavatory by himself. Pulse 50.

Operation. Local anæsthesia. Patient co-operative. An opening was made in the skull just behind the hair line in the right frontal area. When the dura was opened the brain was close up to it and did not pulsate. A spatula passed under the dura released a very small amount of subdural fluid from the parietal region.

A similar opening was made on the left side. A nick in the dura released yellow-brown fluid under tension. The nozzle of a syringe was put into the opening and 10 c.cm. of the fluid was collected. The opening was enlarged and there was a further rush of fluid. The brain appeared normal and lay 1 cm. deep to the dura; it did not pulsate. A piece of thin rubber was inserted as a drain. Immediately after the operation the pulse rate was 48; an hour later it rose to 70. 14th August. Quiet. Less confused. Pulse rate 84. Two days later he was able to be out of bed, knew where he was, answered intelligently. Pulse 80. 20th August. Recovery complete.

The fluid had a protein content of 3·5 per cent.

Case 9.—Q. T., male, aged 54, admitted 7th November, 1940.

Three weeks before admission the patient fell off a bicycle. He was deeply comatose for 24 hours, when he became delirious.

Examination: he was confused and incoherent but could obey commands. He did not know where he was. The tongue was dry. Pulse 80; heart rate irregular 130; extra systoles; hard arteries; blood pressure 120/70; respirations 32; temperature 101° F. Dullness at bases of both lungs. Pupils equal and reacted to light. Limitation of upward gaze left eye. Ptosis of left eyelid. Left facial weakness. Hoffman reflex in left hand. Plantar responses flexor. A line of fracture could be felt extending from the left frontal region to below and behind the left parietal eminence. Fluids were administered. 8th November. Less confused; he could answer questions. Blood urea 90 mg.

Operation. Local anæsthesia. An opening was made above the fracture on the left side, and a large quantity of slightly turbid subdural fluid escaped. The brain did not expand and remained at a depth of 1½ cm. A drain was placed under the dura and brought out through the wound. A similar opening was made on the right side; there was no subdural fluid, and the brain was retracted about 1 cm., but began to expand and pulsated freely, coming up to dural level. A spatula passed between the dura and the brain did not reveal any lesion or any collection of fluid or blood. This wound was closed without drainage.

Next day he was quite conscious and coherent, but did not remember coming to hospital. Heart rate 110, but extra systole every third beat, hence pulse 74. Breathing shallow; passive congestion of lungs; respirations 36; temperature 101·5° F. The drain was partially withdrawn and a large amount of fluid escaped. For the next

three days his mental condition improved, but hypostatic pneumonia developed. 5th November. Mors.

Autopsy. No subdural fluid demonstrated. Brain shrunken, no sign of any lesion on surface or on section.

Case 10.—M. P., male, aged 12, admitted 28th December, 1940, at 7 p.m.

He had been knocked off a bicycle at 4 p.m. that day. He was unconscious for about an hour. On admission he was able to speak sensibly but next morning he did not remember coming into hospital. Pulse 75; blood pressure 105/75; no neurological signs. Next day he felt well. Lumbar puncture, pressure 120 mm. of water. The patient's course was satisfactory in every way. The pulse rate dropped occasionally to 64. A week later he complained of right frontal headache, but next day he did not remember that he had a headache yesterday.

8th January. Severe headache. Lumbar puncture, pressure 180 mm. of water. Pulse 60. The headache was not relieved by the lumbar puncture.

Operation. Right temporal opening. Dura not pulsating. When it was opened a large quantity of clear fluid spurted out, and carried with it at the end some minute clots of blood. The brain lay well below the dura, but began to pulsate in a few minutes and rose to dural level when the boy held his breath or coughed.

Left temporal opening, similar findings but no sign of blood clot.

9th January. Mild headache. Pulse rate 65. Lumbar puncture, pressure 85 mm. of water. Fluids forced. The patient was quite comfortable for the next three days but the pulse rate remained about or below 60.

14th January. Pulse 50. Headache. As the boy had been taking fluids freely and the blood pressure was constant, the wound on the left side was re-opened in search of re-accumulation of fluid. No fluid was present; the brain was shrunken and pulsating freely. A continuous drip (intravenous) of 5 per cent. glucose was given. From this point onwards the patient had no headache. The pulse rate remained about 60 for four days, and on 17th there were several attacks of vomiting. 19th January. Pulse rate rose to 80 and recovery was uninterrupted and complete.

The delay in recovery after operation was probably due to delay in administering a sufficient quantity of fluid.

These cases are summarized in Table 2.

TABLE 2.—*Group II.* SUBDURAL FLUID DURING RECOVERY FROM CONTUSION

NO.	TIME AFTER CONTUSION	MENTAL STATE AND SYMPTOMS	PULSE RATE	LINEAR FRACTURE	RESULT
1	2 months	Traumatic dementia	40→80	+	Good
2	10 days	Confusion, moderate	50	−	Good
3	3 weeks	Confusion, moderate (hypostatic pneumonia)	80	+	Died
4	11 days	Confusion, mild headache	60	+	Good
5	8 days	Clear, headache	60	+	Good
6	12 days	Clear, headache	60 (L.P. pressure, 180 mm. H_2O)	−	Good

Comment

The only clinical feature common to all the cases was a halt at some stage of recovery, the patients remaining in some degree of confusion or suffering

from severe headache. One patient died from hypostatic pneumonia, but in the other five cases progress to recovery was resumed immediately after removal of the subdural fluid.

The patient with pneumonia had a pulse rate of 80 and a heart rate of 130 on admission ten days after the injury; the other patients had or had had pulse rates between 40 and 60. The rate increased immediately after removal of the fluid.

Lumbar puncture was performed in one case and gave a pressure of 180 mm. of water. The tension of the fluid in these cases was not so great as in those of the first group, but the fluid flowed freely and in quantity in each case. In three of the cases the brain remained depressed after removal of the fluid.

These cases suggest that a halt in recovery from contusion associated with a low pulse rate may be due to the presence of subdural fluid, the fluid acting like a " wet blanket " and interfering with the full expansion of the brain which is necessary for the resolution of contusion.

The fact that the patients in this group were not getting worse suggests that the accumulation of subdural fluid had reached its maximum and had stopped. The condition may be classified as a passive " space-occupying " lesion in order to distinguish it from the active expanding lesion found in the patients of the first group. Intracranial hæmorrhage sometimes runs a similar course, and a diagnosis of a space-occupying lesion based on headache and a low pulse rate has led to the discovery of epidural hæmorrhage in one case and of subdural hæmorrhage in another.

GROUP 3.—*Patients suffering from headache, dizziness, and vague symptoms of nervous instability dating from a head injury.*

Case 11.—T. J., male, aged 40, admitted to the Richmond Hospital on 25th May, 1939.

On 28th July, 1938, he fell from a height of 15 ft., his head striking a concrete block. There was a small scalp wound and a depressed fracture of the right parietal bone. He was unconscious for some hours. During the twelve days of his stay in the local hospital he began to suffer from shooting pains in the head, brought on by " visions " of the fall, and occurring just when he was dropping off to sleep. Later the pain occurred more frequently, and was referred to the left parietal region. When he stooped or turned his head rapidly he became dizzy. He was generally nervous and said that he could not sleep.

26th May, 1939. Neurological examination was negative. Radiography showed a depressed fragment of bone about the size of a penny, its outer table being on a level with the inner table of the skull. Union had taken place.

It was thought probable that the dura had been injured at the time of the accident and that the patient's symptoms might be due to adhesions between it and the brain.

30th May. Operation. Local anæsthesia. A small flap was raised and the depressed bone removed. When the dura was opened a considerable quantity of clear fluid escaped and the brain began to pulsate freely. A flap of dura was raised; there were no adhesions, so the dura was closed and the bone replaced. A single burr hole was made in the left parietal region; there was no fluid and the brain lay ¼ in. below dural level.

The patient was delighted with the result of the operation. He was discharged

on 12th June, and on 17th July was re-admitted complaining of soreness about the wound on the right side and dizziness on stooping. The wound was soundly healed, but the replaced bone was loose. He was kept three days in hospital, during which he slept well and made no complaints. He was then reassured and sent home. 28th November, 1939. He was re-admitted because of a discharging sinus in the wound. His symptoms were practically the same as they were on his first admission. 4th December. The bone which had been replaced was necrotic and was removed. He was well and cheerful all the time in hospital and was discharged on 15th December.

3rd July, 1940. Interviewed for insurance purposes. His symptoms were practically the same as when he was first seen. The defect in the skull had not added to them.

Case 12.—M. P., seaman, aged 28, admitted 28th May, 1940.

On 14th February, 1936, he fell about twenty feet on to an iron deck. He was unconscious for a week, and for the first two days violent and delirious. He was then admitted to an Australian hospital and kept for 3½ months. During this time he complained of severe headache, and periods of violence alternated with states of lethargy and sullenness. Improvement was slow, but in May of that year he was sufficiently recovered to return to England.

From this time until admission he complained of headache, poor memory, and dizziness, and frequently stated that he was "finished for life." When in hospital he was sensible and amenable, and it was thought that the headache was genuine. Neurological examination was negative.

Encephalography was discarded because of the attendant discomfort, and the patient agreed to exploratory openings being made in the skull.

30th May, 1940. Operation. An opening was made on the left frontal region. There was a considerable amount of subdural fluid, and when it was removed the brain pulsated more freely; but there also seemed to be an excessive amount of subarachnoid fluid, which suggested that there was a certain amount of cortical atrophy on that side of the brain. A similar opening was made on the right side, but there was less fluid.

Next day the headache was completely relieved.

5th June. Discharged. No headache since operation.

August 1940. A letter was received from his sister: "I cannot say that I see any improvement; he is still irritable and cross at times." Headache was not mentioned.

The cases of group 3 are summarized in Table 3.

TABLE 3.—*Group III*

NO.	CONTUSION	SYMPTOMS	ONSET	TIME ELAPSED BETWEEN OPERATION AND INJURY
1	+	Headache, dizziness, nervous instability	Immediately after recovery	1 year
2	+	do.	do.	4 years
3	+	do.	do.	3½ months
4	+	Headache, poor vision, nervous instability	do.	7 months

Comment

The patients in this group afforded typical examples of the "post-traumatic syndrome" of headache, dizziness, and nervous instability, all had suffered

initial concussion. The impression gained at operation was of a shrunken atrophic brain, with an excess of fluid, both subdural and subarachnoid; there was no tension. The patients stated that the headache had been relieved by the operation, but it was obvious that the nervousness was not diminished, nor were the complaints of dizziness less frequent.

A review of these cases suggests that the post-traumatic syndrome is due to intrinsic cerebral damage inflicted at the moment of the accident. It is possible, however, that the accumulations of fluid may have played a part by preventing the brain from reacting normally to injury. Removal of fluid during the acute stage might have been beneficial, but removal of fluid a long time after the injury could not be expected to improve the condition of the brain. For this reason no further cases of the true post-traumatic syndrome have been submitted to operation.

GROUP 4.—*Patients in whom headache and occasionally some definite nervous symptom, constant for the individual,* started *some time after a head injury.*

The results of operation in this group were better than in any of the others.

Case 13.—R. D., female, aged 20, admitted to Richmond Hospital, Dublin, 18th April, 1940, on account of left frontal headache.

In the beginning of January 1940 she fell off a toboggan and her head struck the ground. She got up immediately. Apart from a momentary sensation of dizziness she felt quite well and only mentioned the fall when directly questioned. At a dance that night she " felt a bit shaky ".

12th April, 1940. She began to complain of an ache all over the head. Two days later the headache became very severe and was confined to the left side; it was throbbing in character.

Examination a week later revealed slight lower facial weakness on the right side, the reflexes of the right leg were slightly increased. There was no Babinski. The pulse rate dropped occasionally to 60. The fundi were normal. The diagnosis of a left frontal subdural hæmatoma was considered.

23rd April. Operation. Local anæsthesia. A small opening was made just behind the hair line in the left frontal region. The dura did not pulsate. When it was opened clear fluid welled up, and more escaped when the spatula was introduced. The brain then began to pulsate freely. Another opening was made in the right posterior parietal region, with similar findings. The headache was relieved and the facial weakness disappeared, but in the course of the next three days the headache returned and the patient became rather drowsy.

27th April. A right frontal opening was made and a larger amount of fluid obtained than from either of the previous openings. Several small clots came away in the fluid. A needle was passed into the right ventricle. There was no tension and the ventriculograms were normal. After this, recovery was uninterrupted and the patient was discharged on 13th May.

She continues free from symptoms.

Case 14.—A. P., male, aged 7, admitted to the Richmond Hospital on 26th January, 1939, because of epileptic attacks.

On the day before admission the boy had a generalized epileptic fit which lasted for three hours There was no warning of the attack. After it, he complained of severe pain in the left side of the head. In the early hours of 26th January he had what was described as a rigor, in which all his limbs were fixed in extension. He was admitted in a condition of status epilepticus, which was ultimately controlled by

luminal. Neurological examination was entirely negative. On direct questioning the parents said that the boy had had a fall on the head " a month or two ago," but that he had not hurt himself as far as they knew. He had always been healthy.

28th January. Encephalography under avertin anæsthesia. The findings were inconclusive, so it was decided to perform ventriculography. For this purpose an opening was made behind the parietal eminence on the left side. When the dura was incised there was a rush of a large quantity of clear fluid under tension. The brain was retracted for about two centimetres and did not expand. The wound was closed.

After this the boy appeared to be perfectly well and there were no fits.

In the course of the next week a small swelling appeared at the site of the wound; it was thought to be a hæmatoma, but on 6th February a needle was passed into it and 20 c.cm. of clear fluid was aspirated. The protein content of the fluid was 40 mg. per 100 c.c.m The fluid did not collect again and the boy was discharged on 26th February. He has continued well and free from attacks.

Case 15.—W. M., married woman, aged 58, admitted to Richmond Hospital on 17th September, 1937, complaining of dizziness, headaches, and an overpowering inclination to sleep.

On 6th August, 1937, she slipped when coming downstairs and she thought that the back of her head struck one of the steps. She felt rather stupid for a moment but she resumed her work immediately. Apart from the attacks of dizziness she was well for nearly a month. Then, during a spasm of coughing, she felt a sharp pain shooting through her head from temple to temple. About the same time there was a sensation of " pins and needles " in both feet. She spent a fortnight in another hospital and had several lumbar punctures.

Examination: the medial aspects of both optic discs were slightly blurred. The only other abnormality was a Babinski reflex on the right side. A subdural hæmatoma was suspected.

18th September. Local anæsthesia. A left temporal opening exposed a tense brain which was not pulsating. A spatula was passed under the dura; clear fluid welled up from every direction, and in a minute or two pulsation of the brain was obvious. When a similar procedure was carried out on the right side fluid under tension escaped when the dura was opened, and the brain did not pulsate until considerably more fluid was released by the spatula. Immediately before the release of fluid on this side the pulse rate was 64; immediately after, it was 80. The patient felt better after these operations for 24 hours, but she then became gradually more drowsy and the pulse rate fell to 60. It was thought that fluid had accumulated again, as the wounds had been closed without drainage. 21st September. Wound on right side opened. There was no fluid and the brain, which was pulsating, had dropped away from the dura for nearly a centimetre. The same condition was found when the left side was exposed. Large amounts of fluid were administered. The patient continued rather drowsy for the next two days, but then began to improve rapidly.

According to recent reports recovery was complete.

Case 16.—N. E., aged 33, admitted 26th January, 1941, on account of headache and occasional attacks of vomiting.

In 1937 the patient, who was captain of a well-known hurley team, was struck by a hurley stick just above the left ear. He was stunned for an instant but continued the game. There was no amnesia and no disability afterwards.

In 1939 the appendix was removed, and shortly afterwards he began to suffer from left-sided headaches. He felt " as though a swelling were moving about above the left ear." He complained of tiredness, unsteadiness, and inability to concentrate.

Nausea was often present, and he had vomited about six times inside two years. He attributed all his troubles to the appendix operation.

On 10th January, 1941, he consulted Dr. Balfe, of Dublin, who found him giggling and laughing and emotionally unstable. General and neurological examination was negative, but radiograms of the skull disclosed large vascular channels and lacunæ in the region of the left coronal suture. These findings suggested the possibility of a meningioma, so the patient was admitted to hospital on 26th January. Next morning he walked out of hospital without telling anyone. Two days later he arrived at his home ninety miles distant, having walked the whole way according to his own statement. He had money in his pocket. He begged his people not to send him to hospital or to let anyone touch him.

This emotional storm soon subsided, but the headache continued and he was re-admitted on 28th April for ventriculography. Neurological examination was negative.

30th April. A needle was passed into the right ventricle; the fluid pressure in the ventricle was 100 mm. of water; 16 c.cm. of fluid were removed and replaced with air. The whole ventricular system appeared normal in the radiograms. An opening was then made in the left temporal region. When the dura was opened there was a gush of fluid from the subdural space, and later a free flow when a spatula was passed under the dura. The brain remained depressed. A piece of thin rubber was inserted as a drain.

After the operation the patient was encouraged to drink freely in order to promote expansion of the brain. During the next 24 hours enough fluid escaped to keep the inner layers of the dressing moist. The drain was then removed and the " waiting stitch " tied. The patient said that the headache was completely relieved.

7th May. Blood pressure remained constant at 138/88. The patient felt well. A careful record of the pulse rate was kept before and after the patient got up; it remained between 50 and 54. Atropine 1/50th gr. did not affect the rate.

9th May. The left temporal wound was re-opened. The brain was bulging into the opening; a spatula was passed but no fluid was found. The wound was closed and magnesium sulphate in hypertonic solution administered by rectum.

11th May. Pulse rate rose from 52 to 68 and, later, when patient got up the pulse rate rose from 66 to 78. Blood pressure 120/80. From this date the pulse rate remained fairly steady between 74 and 84, although it dropped to 54 on one occasion during the night.

25th May. Patient discharged, declaring himself well. From the date of the operation all the emotional symptoms, formerly so obvious, disappeared. A report on 30th June stated that he had resumed work and was perfectly normal.

1st September. The patient was re-admitted for observation. He was definitely psychoneurotic and subject to religious obsessions.

Case 17.—L. H., female, aged 32, employed in a cosmetic factory. Admitted 28th May, 1941, on account of severe headache.

On 1st February, 1941, the car in which the patient was a passenger collided with another car. The patient's head struck a pillar of the car and there was a slight abrasion in the right temporal region. The patient immediately said that she was all right, but in the course of an hour she collapsed and was taken to hospital. After another hour she awoke and insisted on leaving hospital. Next day she returned to work, but had to stop working in about half-an-hour because she felt so " shaky." She stayed in bed for a fortnight. On getting up she began to suffer from severe headaches in the right fronto-temporal region, which were increased by any activity or by stooping. She, however, went back to work, but found that she did " funny things," like giving silly orders, putting the wrong ingredients in cosmetics, or making mistakes in accounts. In April she was treated by dehydration methods for a month, but these produced no improvement.

On admission. Neurological and radiological examination was negative.

29th May. Operation. An opening was made just above the junction of the anterior and middle thirds of the right temporal ridge. The anterior division of the middle meningeal artery crossed the opening. When the dura was opened the brain presented and there seemed to be a certain amount of fluid under the arachnoid. A spatula was passed forwards under the dura and a small amount of subdural fluid escaped. On passing the spatula downwards towards the temporal region fluid flowed freely. A strip of thin rubber was left as a drain in the subdural space.

The headache was completely relieved.

On the fifth day after operation the patient was sitting up, apparently very well, when she got a severe "neuralgic" pain in the region of the wound and fainted. Two hours later the pulse rate fell to 66, but rose soon to its normal rate between 76 and 80. The neuralgic pain continued; it was quite different from the former headache. A week later the pulse rate dropped to 60 for some hours, and because of this and the pain, the wound was re-opened.

A definite adhesion was discovered between the arachnoid and the dura, just at the point where the meningeal artery lay. The slightest touch on the adhesion produced the intense neuralgic pain. The adhesion was divided and the pain disappeared immediately. There was no excess of subdural fluid. Amniotic membrane was tucked under the dura round the opening and the wound closed. Before the patient left the table it was decided to exclude subdural fluid on the opposite side, so an opening was made in the left frontal region just behind the hair line. An excessive amount of subdural fluid flowed out and pulsation of the brain became more marked.

The patient had an occasional slight headache for the next two days, but after that time recovery was complete. There has been no recurrence of symptoms.

25th July. Perfectly well. Complete amnesia for the accident and arrival in hospital.

Case 18.—C. J., male, aged 25, admitted to the Richmond Hospital on 4th January, 1940.

In March 1939 he was struck on the head by a falling tree. The roof of the left orbit was fractured and there was bleeding into the orbit and into the eyelids. He was unconscious for three days.

At the end of three weeks, on his discharge from another hospital, he was well except for a feeling of numbness and tenderness over the left side of the head. In July 1939 he began to complain of severe throbbing headaches, which came on at intervals varying from one to three days and lasting for two or three hours. These headaches were not modified by posture but were increased by effort of any sort.

Examination disclosed anosmia on the left side, but no other neurological symptoms. The patient was not nervous, nor did he seem to exaggerate his symptoms. He had no memory of the accident nor of events some hours before it. He welcomed the suggestion of an exploratory operation.

5th January, 1940. Operation. Local anæsthesia. A small burr hole was made just behind the hair line in the left frontal region. The dura was opened; the brain presented in the opening and did not pulsate. A narrow curved spatula was slipped between the dura and the arachnoid towards the frontal pole of the hemisphere. Clear fluid began to well up freely along the spatula. The flow continued steadily for some minutes. The spatula was then directed towards the temporal region and more fluid escaped. The brain was now pulsating freely. The wound was closed without drainage. From that moment to the time of writing the patient says that he has been free from headache and is quite fit for the work which he has resumed. The operation was done and his acknowledgment of complete relief registered before his claim for compensation was settled.

Case 19.—L. D., male, aged 39, was conductor in a bus which, on 28th July, 1938, hit an electric light standard. His head struck the side of the bus and he became unconscious immediately. He remained unconscious for three days. Recovery was without incident and he was discharged from hospital on 15th September. He resumed work at the end of that month.

He was well for eight months; then he began to get attacks of headache and vomiting which would lay him up for three weeks at a time.

In February 1940 he began to feel that the left foot was turning outwards, but when he looked at it, it was stationary. Later, definite attacks occurred in which the left leg and left arm twitched and the left hand felt numb. Consciousness was lost in one of these attacks. From this time until his admission to the Richmond Hospital on 29th April, 1940, he had one fit, and the headaches continued.

30th April. There was slight unsteadiness in the movements of the left hand. The left limbs were slightly weaker than the right, otherwise neurological examination was negative. After a few days in hospital the patient felt well and decided to go out next day; but next day he was prostrate with intense headache and vomiting. This sequence recurred several times; he then accepted the suggestion of operation.

20th May. Operation. Local anæsthesia. A small burr hole was made in the region of the right parietal eminence. The dura was pulsating. When it was opened and the spatula passed there was a copious flow of clear fluid from the subdural space. Before the wound was closed the arachnoid was seen to be intact and the brain pulsating freely. A similar procedure was carried out on the left side. Here there was a greater quantity of fluid.

Next morning the patient was feeling " great " as he sat up smoking a cigarette. He left hospital on the fifth day. August 1940. Returned to work.

March 1941. The patient reported that he had been at full work since September 1940 and had been quite free from headaches. In December and January he had, however, " fainted," and had to remain in bed on each occasion for three or four days. His story was suggestive of epileptic attacks, but no corroborative evidence could be obtained.

Case 20.—M. G., aged 30 (a patient of Dr. E. L. Murphy and Mr. Harry Meade, and included here by their courtesy).

In 1935 this patient was thrown off a horse and was rendered unconscious immediately. When admitted to hospital he was found to have a right hemiplegia. He remained unconscious for thirteen days and ultimately made a complete recovery, except for some residual weakness of the right side. In the spring of 1940 his behaviour became erratic, and a tendency to exhibitionism developed. He was reported to have attacks in which he would stand and stare, apparently oblivious of his surroundings. He was euphoric, but had been so for an indefinite time.

July 1940. Neurological examination by Dr. Murphy revealed slight right facial weakness of supranuclear type, definite weakness of the right arm and hand, and some spasticity in the right leg. The patient walked with a right hemiplegic gait. All the tendon jerks were exaggerated on the right side, and the right abdominal reflexes were definitely diminished. There was a positive Babinski reflex on the right. Lumbar puncture. Pressure 190 mm. of water. Fluid normal.

25th July. Operation. Local anæsthesia. Mr. Meade made an opening in the left frontal region. When the dura was opened the brain bulged into the opening and did not pulsate. A spatula was passed under the dura and subdural fluid escaped in a steady flow. After some minutes the brain fell away from the opening and began to pulsate freely. The wound was closed.

The chief result of the operation was a cessation of abnormal behaviour. There was also some improvement in the power of the right hand and leg, and the right facial weakness was no longer noticeable. The plantar response was equivocal.

March 1941. There has been no retrogression in his condition up to the present.

Case 21.—D. S., religieuse, aged 24, admitted 12th May, 1941, on account of headache and blindness.

In January 1937 the patient slipped on a polished floor; her head hit the floor and she was unconscious for about twenty minutes. She recovered rapidly, but suffered from occasional and severe headaches for the next six months. In April 1938 she unaccountably slept for six hours beyond her usual time of rising, which was 5.30 a.m. In May 1938 menstruation stopped.

In January 1941 she began to walk in her sleep, and continued to do so for two weeks. In this month there was another incident of prolonged sleep. The patient had always been known in the community to have a small appetite, but, despite this, there was a steady gain in weight. For the last few years she had attacks of vomiting lasting on each occasion for about an hour.

Examination revealed slight obesity; hair distribution normal; weight 8 st. 11 lb.; pulse rate 60; blood pressure 120/80. Gynæcological examination revealed no abnormality. Neurological examination was negative, except for visual acuity of $\frac{6}{18}$ in both eyes, and signs of early papillitis. In the radiograms of the skull there was a suggestion of supra-sellar calcification. Exhaustive metabolic examinations were made, but no abnormality was discovered.

2nd February. Both optic discs showed swelling of 2D. 12th February. Visual acuity O.D. $\frac{6}{12}$, O.S. $\frac{6}{18}$. Small scotoma in nasal field of right eye. Papillœdema 2D. 26th February. Menstruation returned.

21st April. Patient complained of severe right-sided headaches,

3rd May. Intense " bursting " headache. Patient said she could not see during the attacks, which continued to recur two or three times a day until admission.

14th May. Blind, but pupils reacted briskly to light. It was decided that the apparent swelling of the discs represented an anatomical abnormality, and that the blindness was psychogenic. The supra-sellar calcification noted in earlier radiograms

TABLE 4.—*Group IV*

NO.	INITIAL CONCUSSION	SYMPTOMS	ONSET AFTER INJURY	FOCAL SIGNS	TIME BETWEEN OPERATION AND INJURY	RELIEF
1	—	Headache	3 months	Paresis L. vii	3 months	+
2	—	Status epilepticus	2 months	—	2 months	+
3	—	Headache, dizziness	1 month	R. Babinski	1 month	+
4	—	Headache	3 weeks	—	7 years	+
5	—	Headache, emotional	2 years	—	4 years	+
6	+	Headache, memory defects	14 days	—	4 months	+
7	+	Headache	4 months	—	9 months	+
8	+	Headache, vomiting	10 months	L. hemiparesis	1 year and 10 months	+
9	+	Abnormal behaviour	$4\frac{1}{2}$ years	R. hemiparesis	5 years	+
10	+	Headache, hysteria	3 years	—	4 years	+
11	+	Headache	14 days	—	2 months	+
12	+	Headache	$1\frac{1}{2}$ years	—	—	+
		Dizziness, buzzing in ear	Immediately		1 year and 7 months	—

could not be confirmed. Neurological examination was completely negative. The headaches, however, seemed to be genuine and devastating, so ventriculography was advised. An opening was made in the region of the left parietal eminence. The dura was pulsating and there was no tension. Eleven c.cm. of air were injected. The ventricular system appeared normal in the radiograms. It was decided that an operation should be performed at the site of the headache in the right frontal region, partly for psychological reasons and partly because of previous experience of the relation between post-traumatic headache and excess of subdural fluid.

An opening was made just behind the hair line in the right frontal region. When the dura was opened there was a free flow of fluid from the subdural space, the wound, which had a capacity of about 1½ c.cm., filling up ten times, apart from the amount sucked away at the beginning.

The headache was completely relieved and has not recurred. Inside a week the simplest methods of psychotherapy brought vision back to normal. The appearance of the discs did not change.

These cases are summarized in Table 4.

Comment

The constancy of an interval between the injury and the onset of symptoms suggests a lesion of slow development, and the fact that the symptoms continued at their initial level suggests that the lesion had become stationary.

In most of the cases removal of the fluid was followed by freer pulsation of the brain and by the relief of symptoms. In a few, the brain remained depressed after removal of the fluid and the symptoms persisted for a short time.

It is important to distinguish between the cases of this group and those of group 3. In this group the patients, with two exceptions, were mentally stable and complained only of headache. The history and operative findings suggest that the brain had either escaped injury altogether or had recovered from injury before the accumulation of fluid had taken place.

In group 3 the lesion was essentially cerebral; in group 4 essentially extracerebral.

Incidence of Subdural Effusions

The dura mater has been opened and the brain inspected in 63 cases of closed head injury. The operative findings appear in Table 5.

These figures suggest that an excess of subdural fluid is a common lesion in patients who present indications for operation. In this series of cases there is little to suggest that swelling of the brain is usual after injury, or that " unresolved contusion " is of frequent occurrence. It is, of course, impossible to state what conditions obtained in the many patients upon whom operations were not performed.

TABLE 5

	EARLY OPERATION	LATE OPERATION	TOTAL
Massive epidural hæmorrhage ..	6	0	6
Massive subdural hæmorrhage ..	6	8	14
Intracerebral hæmorrhage	1	1	2
Subdural fluid	9	23	32
Meningeal adhesions	0	3	3
Shrunken brain	2	2	4
Swollen brain	1	1	2
	25	38	63

Relation of Subdural Fluid to Post-traumatic Disturbances

Twenty-one of the 38 patients upon whom " late " operations were performed had symptoms persisting or beginning a considerable time after the injury.

The operative findings in these " post-traumatic " cases are summarized in Table 6. Cases of epilepsy are not included.

TABLE 6.—POST-TRAUMATIC DISTURBANCES

SYMPTOMS	LESION FOUND	NO. OF CASES
Headache, dizziness, nervous instability dating from injury.	Cortical atrophy Subarachnoid lakes Subdural fluid	4
Headache with or without a definite nervous symptom, starting after an interval.	(1) Subdural fluid	12
	(2) Swollen brain (" Unresolved contusion," Trotter, 1924).	1
	(3) Shrunken brain	1
Localized headache with dizziness.	Meningeal adhesions (Penfield, 1936).	3
		21

It is clear that post-traumatic disturbances cannot be ascribed to the same lesion in every case.

Origin of the Excess of Subdural Fluid

No conclusions have been reached regarding the origin and the nature of the fluid. It is usually assumed that the arachnoid membrane is torn at the moment of the accident and that cerebrospinal fluid is forced into the subdural space. Peet (1940) suggests that the tear in the arachnoid membrane is valvular

in type, so that the fluid cannot return to the subarachnoid space. That a communication does exist between the subarachnoid and subdural spaces in a certain number of post-traumatic cases has been demonstrated by encephalography on many occasions. Penfield and Norcross (1936) stated that in 18 out of 22 cases in which spinal insufflation of air was employed for the relief of post-traumatic headache the air appeared in the subdural space. Lemere and Barnacle (1936) demonstrated air in the subdural space in 20 per cent. of 800 encephalograms, but they do not state whether the air was found more frequently in the traumatic than in the non-traumatic cases.

The fact that a communication exists so frequently suggests that any excessive amount of subdural fluid is derived from the cerebrospinal fluid. On the other hand, an excess of fluid has been found in the subdural space when no communication with the subarachnoid space has been demonstrated.

Another speculation regarding the origin of the fluid may be made. The subdural space normally contains a certain amount of fluid, and it is reasonable to suppose that this amount may be increased under the influence of appropriate stimuli, and that an effusion analogous to that in a pleural, peritoneal, or joint cavity may take place. Such an effusion occurs when infection is introduced into the subdural space. The writer has observed an empyema of the space following a fracture involving an infected frontal sinus; the amount of pus present seemed much greater than any amount which the frontal sinus itself could contain. Courville and Blomquist (1941) have described similar cases. A traumatic effusion from the dura appears to be within the bounds of possibility, and such a conception is not incompatible with the clinical course of the cases reported above.

It is usually difficult to collect sufficient fluid uncontaminated with blood to make accurate estimations of the protein content. In the three cases in which satisfactory estimations were made the protein content was 180, 3,500, and 40 mg. per 100 c.cm. Although it is always possible that the high amounts of protein were due to an initial mixture of blood and cerebrospinal fluid (" fluid hæmatomas," Munro, 1940), it is also possible that they indicated a true effusion.

Confirmation of the Diagnosis

Estimations of spinal fluid pressure have not assisted in the diagnosis.

Ventriculography has not revealed the presence of even considerable amounts of fluid in the subdural space. Encephalography has been regarded as a more traumatic performance than the making of twin burr holes. In short, an amount of subdural fluid sufficient to be responsible for the patient's symptoms may escape detection by any method short of opening the dura mater.

It is recognized that observations of a minute area of the meninges and brain yield but a small amount of information, nevertheless such information may be impossible to obtain by less direct methods.

Operative Procedures

Local anæsthesia is used when possible.

When middle meningeal hæmorrhage is suspected, as it is in most of the early cases, the skull is opened just above the highest part of the temporal crest. The incision in the scalp may be either vertical or horizontal, but it should form a section of whatever incision would be used if a middle meningeal hæmorrhage were found. The length of the incision is about one inch, and it is kept open and dry by a self-retaining mastoid retractor. The bone is opened by Hudson's drill, the conical burr determining the size of the opening in the inner table. The edges of the opening are bevelled with the spherical burr. If extradural hæmorrhage be found, the wound is enlarged and the necessary amount of bone removed towards the base of the skull. If no extradural blood be seen, the dura is opened. Subdural fluid or blood may escape. A curved instrument like Adson's raspatory is passed under the dura, its end keeping close to the bone. Any epidural hæmorrhage pushes the dura inwards, and this displacement can be appreciated when passing the instrument. The pressure of the instrument towards the bone may squeeze epidural blood into the opening. It is safer to search for epidural blood in this way than to pass an instrument between the bone and the dura—a procedure which may start bleeding. If subdural fluid or blood be found in these acute cases it is not necessary to enlarge the opening in the skull. When the brain does not expand, a twisted strip of thin rubber is left as a drain in the subdural space, its other end lying under the scalp. The wound is closed completely. If fluid be found on one side, the whole procedure is repeated on the other side of the skull. In the chronic cases exploration is conveniently carried out through openings made at the sites for ventricular puncture, so that ventriculograms may be made if necessary.

It is important that no " hole in the head " should be left to form the foundation of extravagant claims afterwards. The opening in the skull need be no larger than that obtained with the conical portion of Hudson's drill. A small trephine button can be replaced. Even without attempts at occlusion it is usually difficult to find the site of operation in the course of a few weeks.

Summary

A subdural effusion has been found in nine out of twenty-five cases of acute head injury. The fluid seemed to act as an expanding lesion of the same order as the massive hæmorrhages.

A subdural effusion has been found in twenty-three out of thirty-eight cases of head injury after the acute stage had passed. The fluid appeared to constitute a passive space-occupying lesion which retarded rather than jeopardized recovery.

The expanding type of effusion was found in two, and the space-occupying type in five, patients who had not suffered from concussion nor given any clinical sign of cerebral damage.

An attempt has been made to indicate what type of post-traumatic disturbance is amenable to surgery.

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THE SIGNIFICANCE OF AN ABNORMAL ELECTRO-ENCEPHALOGRAM

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ATTENTION has recently been focused upon the occurrence of abnormalities in the electro-encephalogram (e.e.g.) of apparently normal subjects, and upon the high incidence of these abnormalities in subjects with behaviour disturbances and in other members of their families. Davis (1941) analysed the variations in the e.e.g. of groups of normal subjects and the abnormalities in wave form and frequency which she found in epileptic and psychotic patients. Similarly Lindsley and Cutts (1940) measured the number of waves in different frequency bands in small groups of normal adults and children, and in groups of children considered to be " constitutionally inferior " or presenting definite behaviour problems. Previously Jasper, Solomon, and Bradley (1938) had studied the abnormalities seen in the e.e.g. of behaviour problem children, while Hoagland, Cameron, and Rubin (1937), and Davis and Davis (1939) showed that a relatively high proportion of psychotic, especially schizophrenic, patients had abnormal e.e.g.'s.

In a statistical evaluation of the e.e.g. in epilepsy made by Golla, Graham, and Walter (1937), abnormalities were found in the e.e.g.'s of 60 per cent. of a mixed group of epileptics. It has since then been generally accepted as the common experience of most workers that a proportion of undoubted epileptics have a normal e.e.g. between fits. Jasper and Kershman (1941) have recently reported abnormalities in the e.e.g.'s of over 95 per cent. of a large group of epileptic subjects, and in surveying the electro-encephalographic phenomena found in epilepsy they have excluded epileptic subjects with " normal " records as being atypical. Lennox, Gibbs and Gibbs (1940) found that with their methods of interpreting records about 3 per cent. of patients with overt seizures had normal e.e.g.'s. This discrepancy in the percentage abnormality rate of epileptics may possibly be due to a difference in the norm adopted, but as there are not comparable figures for control groups of normals in all the communications this point is obscure. Löwenbach (1939), Strauss, Rahm, and Barrera (1939), and Lennox, Gibbs, and Gibbs (1939 and 1940) have

carried the investigation into the families of epileptic subjects. All these workers demonstrated a high incidence of abnormal e.e.g.'s in the members of these abnormal families. In particular Lennox, Gibbs, and Gibbs (1940) found that although they considered the e.e.g. definitely abnormal in 10 per cent. of a group of otherwise normal subjects upon the basis of a norm which they defined, it was abnormal in 60 per cent. of the near relatives of epileptics, while 95 per cent. of the epileptic subjects were found to have one or more parents with an abnormal e.e.g., although only 20 per cent. gave a family history of epilepsy. Williams (1941*b*) compared the percentage abnormality in the e.e.g. of a group of normals with that of subjects suffering from a post-traumatic syndrome, the figures for the two groups being 8 and 50 per cent. The percentage abnormality was found to be three times as high in a group of psychoneurotics, and six times as high in a group with organic cerebral damage as in the normal group. Davis (1941) dealt with the definition of the normal in detail. She compared the characteristic features of the e.e.g. of groups of fully investigated normal subjects with those of subjects with an unknown past history, of unstable subjects living at home, and of patients in a mental hospital, and she was able to demonstrate an ascending scale of abnormality in these groups. Lindsley and Cutts (1940) found a similar ascending scale of abnormality in the e.e.g.'s of their groups of normal and abnormal children.

There is now close agreement between different workers upon the criteria selected in establishing the norm of the human e.e.g., but however meticulous the definition the limits of normality are so wide, the degrees of abnormality so variable, and the e.e.g. record itself so complex, that subjective interpretation becomes inevitable. In order to compare the results from different laboratories it is therefore necessary not only to specify the recording technique and the criteria of abnormality adopted, but also to apply these criteria to comparable groups of subjects. Furthermore the true biological significance of a single abnormal e.e.g. can only be assessed in relation to the percentage abnormality of the group. For example, the significance of a normal e.e.g. in a suspected epileptic is considerably greater if its incidence is less than 5 per cent. (Jasper and Kershman, 1941) and not 40 per cent. (Golla, Graham, and Walter, 1937), while the importance of an abnormal e.e.g. in a normal subject becomes much greater if it is possible by qualitative selection of normals to alter the quality of the e.e.g.'s in the selected groups. It is therefore necessary to have a constant and well defined norm in order to appreciate the implications of the deviation from that norm of any subject or group of subjects.

This present survey, which is based upon clinical and electro-encephalographic examination of 900 subjects, was undertaken with this necessity in mind. Its main purpose was to determine the relative significance of an abnormal e.e.g. in groups of normal subjects and in abnormal states, especially epilepsy. The value of the abnormal changes produced by overbreathing was assessed in relation to the abnormalities seen at rest.

METHOD

A standard three-channel ink-writing electro-encephalograph with condenser coupled amplifiers (Grass) was used. Time was marked in seconds, the paper speed being 1 inch per second. The amplification was maintained as nearly as possible at 1 cm. deflection for 50μV applied to the input. The time constant $\left(\frac{1}{e}\right)$ of the apparatus was 1·1 second, the high frequency filter being maintained at position "3." This position appears to be standard in most laboratories using the Grass apparatus, and gives almost linear reproduction of frequencies between 1 and 50 cycles. These amplifier characteristics were used throughout, no system of filters, similar to those used by Davis (1941), being employed.

The recording technique, electrodes, and electrode placement, which do not differ fundamentally from those of most other workers in the same field, have already been described in detail (Williams, 1941*a*). The recording time was not less than 10 minutes, but was longer when an abnormality was encountered. Lennox, Gibbs, and Gibbs (1940) employed 20 minutes as a minimum, and Jasper and Kershman (1941) 30 minutes. Previous experience had shown that the longer periods of recording, obviously desirable but not always practicable, increase the likelihood in epileptics of observing a subclinical outburst, but it did not so greatly increase the incidence of slight abnormalities occurring in the resting or "between seizure" record.

Except in some of the psychoneurotic group, a period of hyperventilation was employed in all cases after records had been completed with the subject in the resting state. The subject overbreathed for 90 to 120 seconds, depending upon the respiratory exchange and the consequent change in the e.e.g. The record was continued after overbreathing had ceased until it had returned to its resting condition.

MATERIAL

Nine hundred and one subjects were studied. They were grouped as in Table 1:—

TABLE 1

Highly selected normals. (R.A.F. air crew at the completion of flying training)	100
Selected and known normals. (R.A.M.C. and V.A.D. personnel)	121
Psychoneurotics	148
Post-traumatic states—	
Over 3 months	132
1–3 months	105
Less than 1 month	100
Epileptics—	
All types	195
Clinically grand mal.	131
,, petit mal.	25
,, psychomotor	29
,, mixed	10

These subjects were all adults between the ages of 18 and 50, the great majority being in the third decade.

SELECTION OF MATERIAL

Clinical

Normals.—The R.A.F. flying personnel having passed the requisite medical and vocational tests had completed full operational training, and the more unstable and less efficient had thereby been selectively eliminated. Their medical documents were all scrutinized and the family history checked. The R.A.M.C. and V.A.D. personnel had undergone a less rigorous medical and environmental selection, but they had all been on active service for at least a year. The medical documents of this group were also examined.

Abnormals.—The psychoneurotic group were inpatients and outpatients in whom no organic abnormality could be found, but whose symptoms were thought to be psychological in origin. They were mostly constitutionally inferior people, with a personal or family history of instability. None were classed as psychopathic personalities or psychotics, and in a third of the cases no definite evidence of previous instability could be found, the precipitating causes of the illness being mainly exogenous. A few had had a trivial head injury or other illness to which the symptoms had been attributed. The groups of patients with post-traumatic symptoms have already been dealt with in detail (Williams, 1941*a* and *b*).

The subjects of epilepsy were inpatients and outpatients. The clinical diagnosis was made on the accounts given by the patients and other witnesses, but very few fits were witnessed in hospital, and it is fully realized that the differentiation into grand mal, petit mal, and psychomotor epilepsy is probably not so clear cut as the tabulated figures suggest. It was important, nevertheless, in spite of its limitations to handle the clinical evidence in a strictly impartial manner.

Electro-encephalography

The records were examined by two observers without reference to the clinical classification. At first, groups of doubtful normals and doubtful abnormals were isolated, but in order to clarify the issue these doubtful records were re-examined and a definite opinion of their status was given. This seemed more desirable than to have an indeterminate sub-group in each group of cases. The records at rest and after overbreathing were assessed separately.

Evaluation of the E.e.g.—The criteria of abnormality were adopted arbitrarily from a standard acquired during observations made in the past five years. Although largely independent, they are very similar to those described by Lennox, Gibbs, and Gibbs (1940) and Davis (1941), and in most particulars they coincide with those of Jasper and Kershman (1941). Random isolated fast waves of relatively high voltage, or runs of high voltage 10 a second waves were not included in the group of undoubted abnormalities. The selection was rather more rigid than that of Strauss, Rahm, and Barrera (1939).

The criteria are briefly tabulated below, but as has been stated previously,

subjective interpretation is inevitable, for the character of the whole record must be observed. Unfortunately this aspect of selection requires experience, apart from measurement of individual wave forms, which can be achieved with great accuracy by the method of electrical wave band analysis devised by Grass and Gibbs (1938).

Abnormal Features.

1. *At Rest.*—

(i) A dominant frequency, if present, of less than 8 a second.

(ii) A very unstable or asymmetrical dominant frequency.

(iii) Disorganization of the dominant frequency by equally high voltage slower waves.

(iv) A sequence of two or more waves with a frequency of less than 8 a second and an amplitude of more than half that of the dominant frequency in any lead. This includes all subclinical epileptic outbursts, and all general or local runs of slow waves, whatever their form.

(v) Bursts of waves with any frequency over 14 a second whose voltage reaches more than half that of the dominant frequency.

(vi) Random solitary waves with a frequency of less than 8 a second and a voltage greater than that of the dominant frequency from any lead.

Features which enhance the degree of abnormality are waves of long period, high voltage, and episodic or frequent occurrence. Abnormal wave forms have so frequently been illustrated in normal and abnormal subjects (Lennox, Gibbs, and Gibbs, 1940; Davis, 1941; Jasper and Kershman, 1941; Williams, 1941*b*) that no further example is necessary.

2. *After Hyperventilation.*—The only disturbance considered abnormal during a period of overbreathing was the appearance of typical epileptic outbursts of high voltage 2 or 3 a second sine waves, 2 to 3 a second wave and spike formations, 2 a second wave and hump formations or rhythmic outbursts of faster waves of an epileptic type (Gibbs, 1939). The response of the normal e.e.g. to changes in the *p*H of cerebral blood may be so great (Gibbs, Williams, and Gibbs, 1940) that no more rigid standard of abnormality than this could be adopted.

When overbreathing had ceased the record rapidly began to return to its former state. Any paroxysmal outbursts of waves of higher voltage or longer period which occurred after this improvement had begun were considered abnormal. These outbursts, common in epilepsy, usually began between 8 and 12 seconds after the cessation of overbreathing, with the readjustment in the acid base balance (Nims *et al.*, 1940). They were of the following types:—

(*a*) Pure repetitive wave forms, usually of 2 or 3 a second, sometimes up to 6 or 7 a second.

(*b*) Repetitive patterns—2 to 3 a second wave-and-spike or wave-and-hump.

(*c*) Irregular discharges of many abnormally slow waves with varying wave form, voltage, and frequency.

(*d*) A sudden increase in voltage of existing slow frequencies.

(*e*) Very rarely a superimposition of fast waves (25 a second or more).

(*f*) Persistance of the hyperventilation effect for more than 20 seconds after overbreathing had ceased.

Examples of these changes are illustrated (Fig. 1).

RESULTS

The results are presented in Table 2. The incidence of abnormal records in each group is expressed as a percentage of the total, the nearest unit percentage being stated.

TABLE 2

GROUP	NUMBER	PERCENTAGE WITH ABNORMAL E.E.G.'S		PERCENTAGE ABNORMAL AT REST AND AFTER OVERBREATHING
		RESTING	AFTER OVER-BREATHING	
Normal—				
Flying personnel	100	5	5	80
Army personnel	121	10	9	73
Psychoneurotic	148	26	—	—
Post-traumatic states—				
Chronic (over 3 months)	132	40	20	78
Subacute (1–3 months)	105	43	11	83
Acute (to 1 month)	100	58	31	84
Epilepsy—				
Total	195	60	55	73
Grand mal	131	55	50	72
Petit mal	25	60	72	61
Psychomotor	29	83	62	77
Mixed	10	90	80	87

DISCUSSION

The Norm.—The basis of the norm adopted in this investigation has already been described, and the proportion of otherwise normal subjects who attain to it is similar to that found by other workers in the same field. This is more significant because Davis (1941), Lindsley and Cutts (1940), and Lennox Gibbs, and Gibbs (1940) and the present author have each used different, methods of analysing the abnormal features they observed. The agreement of these workers has further significance because the limits of the normal e.e.g. are wide and ill defined, and its features are so complex that the experimental error of selection might be expected to be great. It is therefore apparent that

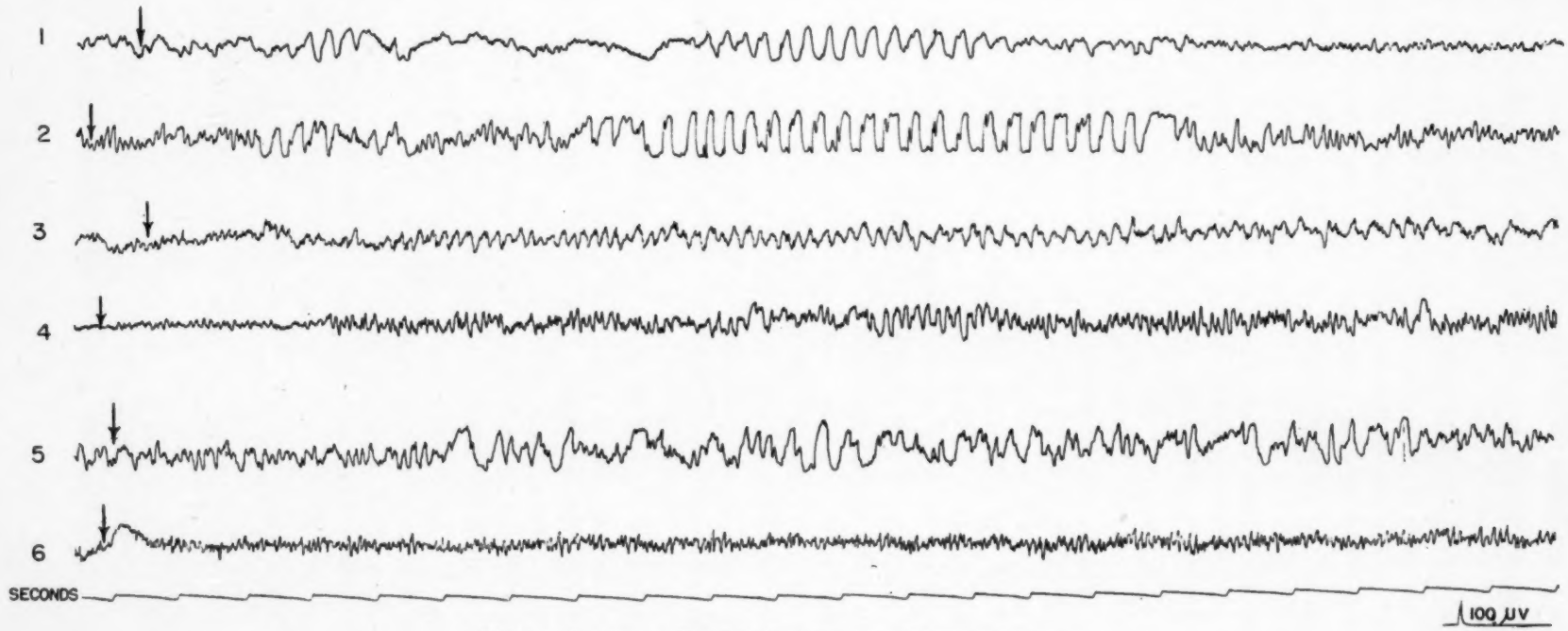

Fig. 1.—Abnormal Types of Response to Hyperventilation.

Portions of the electro-encephalographic records from six subjects. In each case the arrow indicates cessation of 90 seconds of strenuous overbreathing. The samples show:—

1. A run of 3-a-second sine waves beginning 9 seconds after overbreathing had ceased.
2. Wave-and-spike activity beginning 9 seconds after.
3. A prolonged outburst of 6-a-second sine waves gradually slowing to 5, 4, 3, and then 2 a second.
4. An irregular outburst made up of a 7-a-second rhythm, well seen 11 seconds after overbreathing had ceased, with much irregular fast activity.
5. A long run of irregular slow waves of higher voltage than at the end of overbreathing.
6. Persistent activity with a frequency of 24 a second.

the norm is sufficiently distinct to permit an evaluation of the significance of the abnormal e.e.g.

Psychoneurosis.—The psychoneurotic subjects of this investigation are all grouped together, but obviously in some the constitutional factor in the neurosis predominated, while in others, probably a minority, exogenous factors were mainly responsible for it. The increase in the percentage abnormality of the e.e.g. from 10 per cent. of the normal group to 26 per cent. of the psychoneurotic reflects the presence of a constitutional abnormality in these subjects, since there is no evidence at all that psychological trauma can produce abnormal changes in the pattern of cerebral electrical potentials. On the contrary, Jasper, Solomon, and Bradley (1938); Gibbs, Gibbs, and Lennox (1938); and Lindsley and Cutts (1940), have shown that in problem children and even in the children of constitutionally inferior families the incidence of abnormalities in the e.e.g. is high. These children will furnish some of the constitutional psychoneurotics and psychopaths of their generation, and it is apparent that the high incidence of abnormal e.e.g.'s in unstable individuals, as well as in psychotics (Hoagland, Cameron, and Rubin, 1937) is related to the similar abnormalities seen in unstable and constitutionally abnormal children.

Epilepsy.—In epilepsy the position of the abnormal e.e.g. can be more clearly defined. The proportion of abnormal e.e.g.'s observed in this present series is very similar to that recorded by Golla, Graham, and Walter (1937), but it is lower than that found by Lennox, Gibbs and Gibbs (1940), and by Jasper and Kershman (1941). Although all the records were examined in the knowledge of this work, such a constant appearance of abnormality could not be observed in this series of epileptics, on the basis of the norm which had been adopted. On the contrary individual cases showed a great disparity between a profound clinical manifestation of epilepsy and an absolutely normal e.e.g. For example, a man of 22 (Case 320) had had fits since his second year, and he was having several grand mal attacks a month and at least two petit mal each day when examined. His mother, three siblings and one maternal sibling had epilepsy, but his e.e.g. showed a well sustained 10-a-second rhythm with normal characteristics, without any evidence of subclinical outbursts or of an abnormal response to hyperventilation.

The present observations are concerned with the incidence of " between seizure " abnormalities, including the presence of subclinical outbursts, so that the actual wave form encountered in clinical attacks has not been mentioned. Jasper and Kershman (1941) have recommended that Gibbs, Gibbs, and Lennox's (1937) division of epilepsy upon the basis of the e.e.g. into grand mal, petit mal, and psychomotor epilepsy, should be discarded because so many subjects who show specific types of disturbance do not have a similar constant type of clinical attack, so that the form of clinical seizure cannot be accurately predicted from the form of the e.e.g. They point out, for instance, that a subject of grand mal attacks may only show 3 a second wave-and-spike outbursts of the type seen in the e.e.g. in association with petit mal epilepsy. They have therefore analysed the epileptic disturbances

seen in the e.e.g. upon the basis of the wave forms and their cerebral localizations, without reference to the clinical form of epilepsy. This dissociation of the electro-encephalographic diagnosis from the clinical makes for lucidity, and is desirable, but the authors have neglected the fundamental observations made by Gibbs, Gibbs, and Lennox, that when an observed attack which could be recognized clinically as grand mal, petit mal, or an "epileptic equivalent" was associated with a disturbance in the e.e.g., the electrical disturbance was always true to type and was unmistakable (Gibbs, Gibbs, and Lennox, 1937). Thus the division of the electro-encephalographic phenomena, on the basis of their clinical correlates, into the three main types of epilepsy was perfectly valid, and must obviously remain. Jasper and Kershman's observations of the frequent lack of correlation between the form of the subclinical outbursts and the clinical fits which happen to be seen in any subject have repeatedly been made during the present investigations, and were the principal reason for the study of the effects of overbreathing. Gibbs (1939) wrote: "It is my policy to let the diagnosis depend largely on the clinical history and to report that the record shows the type of disorder seen during a particular type of seizure, grand mal, petit mal, or psychomotor." That has become the policy in this laboratory. A full clinical history is obtained and the presence of any abnormal wave form in the e.e.g., whether general or local, is ascertained. In many instances it is possible, in view of specific wave forms or rhythms, to describe the e.e.g. as typically epileptic. In this way the clinical diagnosis of epilepsy may be confirmed in 60 per cent. of the subjects, but the type of seizure resulting from the basic abnormality reflected in the e.e.g. is determined by clinical methods. When a report is given upon the remaining epileptic subjects who have normal e.e.g.'s it is clearly stated that the absence of demonstrable abnormality does not invalidate the clinical diagnosis of epilepsy. The most exact procedure seems therefore to be to establish a nonspecific diagnosis of epilepsy upon the findings in the e.e.g., when abnormalities are observed in a suspected epileptic, but to determine the type of epilepsy by clinical observation.

Hyperventilation.—The abnormal responses to hyperventilation which have been described occur in about the same proportion of the subjects as do abnormalities in the resting e.e.g., and there is about a 75 per cent. overlap in the incidence of the two types of abnormality in all the groups of subjects. This shows that the paroxysmal outbursts, which occur during the period of acid-base readjustment (Nims *et al.*, 1940), are usually related to some underlying metabolic abnormality of cerebral tissue, which is manifest in the dysrhythmia. The presence of these paroxysmal outbursts in each group of subjects indicates that they are not specifically epileptic, but rather that they are related to the underlying cerebral instability which seems to determine the appearance of epilepsy, psychopathy, or neurotic instability. The use of overbreathing to elicit the abnormality increases the likelihood of demonstrating an inborn constitutional defect in potentially abnormal subjects. Experience has shown that greatest instability after overbreathing is present in those

subjects who have normal or abnormal rhythms of high voltage in the resting e.e.g. This forms a link with the known lability of the wave-and-spike pattern in its response to changes in blood CO_2 tension, for this pattern is almost always associated with a well marked dominant frequency. The abnormal responses to overbreathing, particularly the wave-and-spike pattern, can readily be inhibited by a rise in blood sugar, so that the relationship of the investigation to the preceding meal should be noted in doubtful cases. It appeared from critical examination of the material, that the more rhythmic the disturbance after overbreathing, as, for instance, the wave-and-spike formation or rhythms of pure sine waves, the more likely was it to be associated with clinical epilepsy.

The Normal Groups.—Probably the most interesting data in Table 2 are those referring to the normal groups. These show that the incidence of abnormality in a perfectly normal group of subjects may be halved by further selection upon criteria having no apparent relationship to electro-encephalographic selection. These criteria were to some extent based upon medical examination, but both normal groups were selected by this means. The most important single difference between the two normal groups was the occupational stress to which the first group had been subjected. This stress, by causing the eradication of the less efficient and more unstable members of the group, had given rise to a group of relatively super-normal individuals by auto-selection. It thus appears that in at least half of the normal subjects with an abnormal e.e.g. the abnormality may have significance in terms of latent constitutional inferiority. Two of the five airmen with abnormal e.e.g.'s showed changes considered to be definitely epileptic, but they denied personal or family histories of faints or fits, and their work performance had been good. On the basis of the investigations into the heredity of epilepsy, notably that of Lennox, Gibbs, and Gibbs (1940) it is reasonable to conclude that they carry the genetic predisposition to epilepsy which may become clinically evident in their progeny, or even perhaps in themselves. Three of these highly selected hundred normal subjects therefore remain with inexplicably abnormal e.e.g.'s. It may be impossible for practical reasons to show that the dysrhythmia in these cases represents a latent constitutional defect, but the series of observations upon constitutionally inferior children, psychoneurotics, and the near relatives of abnormal individuals, to which reference has already been made, make it very likely that such is the case. In conclusion it may therefore be affirmed that the evidence of this investigation, co-ordinated with that of others, strongly suggests that an abnormal e.e.g., based upon a norm which excludes 10 per cent. of the healthy population, indicates an inborn constitutional defect which may find expression as epilepsy or a behaviour disorder such as a constitutional psychoneurosis, psychopathy, or psychosis, in the subject himself or his offspring.

SUMMARY

The electro-encephalograms of 900 subjects, divided into groups of highly selected normals, normals, psychoneurotics, epileptics, and subjects of a post-traumatic syndrome have been examined. The percentage abnormality has been determined, the subjects being at rest and having overbreathed, upon the basis of arbitrary norms which have been described.

The abnormality rate, detailed in Table 2, varied from 5 per cent. in the highly selected normal group to 60 per cent. in the epileptic. Seventy-five per cent. of the subjects with an abnormal response to overbreathing showed abnormality in the resting e.e.g. The percentage abnormality in epilepsy ranged from 55 in subjects of grand mal to 90 in patients with more than one type of fit. It is suggested that a non-specific diagnosis of epilepsy should be made upon the abnormalities seen in the e.e.g. at rest and after overbreathing, but that the recognition of the specific type of fit should be based on clinical observation.

On the basis of the present results and those of other workers it is concluded that:—

1. An abnormal e.e.g. in an otherwise normal subject is strong evidence of an inborn constitutional abnormality involving the central nervous system.

2. This abnormality appears to be non-specific, and may manifest itself in the subject or his offspring as a behaviour disturbance which may be psychoneurotic, psychopathic, psychotic, or epileptic in type.

3. On the basis of a norm which excludes 10 per cent. of apparently normal subjects, 40 per cent. of epileptics have a normal e.e.g. between fits, but the incidence of abnormality in epileptics showing more than one type of clinical fit was 90 per cent. The significance of this figure is discussed in relation to the findings of other investigators.

I have pleasure in thanking Miss J. K. Reynell, B.Sc., for much technical assistance and for having helped in the selection of the material. I am also grateful to Lieut.-Colonel G. O. Chambers, M.C., R.A.M.C., for permission to publish the data included in this paper, and to Air-Marshal Sir Harold Whittingham, K.B.E., and the Commanding Officers of the Stations concerned for enabling the flying personnel to be investigated. The electro-encephalographic apparatus was lent to the Royal Air Force by the National Hospital, Queen Square, and a grant towards the expense of this work was made by the Medical Research Council.

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SOCIETY OF BRITISH NEUROLOGICAL SURGEONS

28TH MEETING

Held in Oxford, 20th July, 1941

PRESIDENT: MR. NORMAN DOTT

1. Head Injuries from a Physicist's Point of View. (H. Holbourn.)

H. HOLBOURN: It was pointed out that the force which produced the maximum distortion of the brain was the shearing type and that this is produced by sharp rotation of the head. When this occurs, the maximum movement takes place at the surface of the brain. If the skull is violently flexed or extended on the neck, the shearing action has its maximum action on the under-surface of the brain. The temporal pole is brought into violent contact with the lesser wing of the sphenoid and this is where the middle cerebral arteries are. A pure transverse movement does not produce distortion. Professional footballers use this fact when heading a ball. They take the blow on the top of the forehead, so that the direction of the force falls in line with the fulcrum and the centre of gravity of the head thus producing no rotation. A blow between the eyes causes the maximum distortion and is the easiest way of killing. If there is a slow acceleration, such as might be produced by a fall on to a sharp spike, there is not much shearing and the maximum damage is local. Conversely, sudden rotation with rapid acceleration will cause more widespread damage.

G. JEFFERSON recalled the early work on the pathogenesis of head injuries, especially referring to the theory of oscillation in the elipse of Mariotte 200 years ago. No one spoke any longer of oscillations nor knew whether they were important. Gama had experimented with gels 100 years ago, but had not discovered the shearing factor that Mr. Holbourn had shown so clearly, though his results otherwise were the same. Kocher and Ferrari had buried cover-glasses in the brain and found that only the superficial ones could be broken. In each age surgeons had very rightly attempted to apply the physical knowledge of their times to these problems. We must turn to them again.

2. Pathology of Closed Head Injuries in the Acute State. (H. Cairns.)

H. CAIRNS: There is a strong temptation to regard each new type of lesion discovered in the brain in head injuries as the cause of concussion, but the morbid histology of this condition is still unknown. This is not surprising when we consider how easily the state of consciousness is modified by drugs, acute blood-loss, sepsis, and so forth. Present methods are not adequate to display structural changes in the brain in such easily reversible disturbances.

About 80 per cent. of head injuries are uncomplicated cases of the concussion syndrome. It is in the 20 per cent. of unusual cases that the pathology is of particular interest. The fact that there are so many negative explorations for subdural hæmatoma is by no means to be condemned in the present state of knowledge, for it indicates that there is still much to learn of the pathology of the unusual head injuries in relation to the clinical states.

The following pathological changes in the circulation were described:—

1. Obstruction to the internal carotid artery in the neck producing hemiplegia after head injury.
2. Traumatic rupture of the internal carotid artery in the subdural space.

3. Hæmorrhagic necrosis of part of the frontal lobe, due to fibrinoid necrosis and thrombosis of the perforating arterioles. This is a type of lesion associated with temporary or permanent hemiplegia coming on soon after head injury, sometimes without fracture of the skull. In the early stage there is slight narrowing of the corresponding lateral ventricle; later, whether or not there has been spontaneous recovery of the hemiplegia, the body and anterior horn of the ventricle show diffuse dilatation.
4. Focal cortical and subcortical hæmorrhage. The lesion is a congeries of berry-like hæmorrhages, one at the summit of each of several adjacent convolutions. There is no deformity of the ventricle, but there may be focal signs, and these show prompt improvement after operation to remove the clots. The cases so far operated on have been cases of aphasia.
5. Delayed cerebral or subarachnoid hæmorrhage.
6. Traumatic venous thrombosis has been found in several fatal cases associated with swelling of a cerebral hemisphere. The clinical picture does not appear to be distinctive.
7. Rupture of the veins of Labbe and Trolard.
8. Fat emboli in the vessels of the choroid plexus and of the brain. This has been described by Dorothy Russell.

3. Observations of Operations on Closed Head Injuries with Special Reference to Subdural Hydroma. (A. A. McConnell.)

A. A. McCONNELL: In cases in which the headache commenced some time after the injury, there were six cases that had not been concussed and six cases following concussion. A subdural collection of fluid appeared to be responsible for delay in recovery, because symptoms subsided after removal of the fluid (see p. 237).

4. Increased Permeability of the Arachnoid following Head Injury. (H. Heyl and J. Small.)

H. HEYL AND J. SMALL: The paper described the occurrence of non-cystic fluid in the subdural space following head injury. Eleven cases were cited from a series of 74 head injuries treated in the previous six months, the following observations being made:

The phenomenon reported was found to occur both in closed and open head injuries. The fluid was in some cases present bilaterally while in others free fluid was present on one side, and encysted hydroma or hæmatoma on the other. Most of the cases developed evidences of increased intracranial pressure two or three weeks after the head injury, the physical findings being diffuse pyramidal signs, mild papill-œdema (often unilateral), speech defects, abnormalities of tongue movement, 6th and 7th nerve paresis, and increased spinal fluid pressure. On opening the dura, xanthochromic fluid escaped, followed by a persistent welling up of fluid, most of which was seen to be sweating from the subarachnoid space through an intact arachnoid mater. Following the escape of this fluid, the previously tense brain gradually receded from the surface, and normal pulsation commenced.

Study of this subdural fluid has demonstrated that the protein content has always been raised above that of the subarachnoid fluid obtained either by ventricular tap or lumbar puncture. In one case, for example, the protein content of the ventricular fluid was 25 mgr. per cent., of the fluid in the lumbar subarachnoid space 30 mgr. per cent., and of the subdural fluid 150 mgr. per cent.

To account for the presence of this subdural fluid and the sweating of fluid through the arachnoid is to theorize: it may be due either to an increased permeability of the arachnoid or an osmotic attraction of cerebro-spinal fluid through the arachnoid mater caused by the high protein content in the subdural space resulting from bleeding

at the time of the injury. It was suggested that the rate of recovery of these patients was accelerated by the utilization of burr-hole drainage of this fluid.

5. Traumatic Porencephaly. (M. A. Falconer and Dorothy Russell.)

M. A. FALCONER AND DOROTHY RUSSELL:

6. Fat Embolism. (Dorothy Russell.)

DOROTHY RUSSELL: Out of 125 fatal accidents 41 showed evidence of fat embolism and in 29 this was the major cause of death. In six cases there was no bony injury. (Robb. Smith, 1941). Cerebral fat embolism may complicate the picture in head injury. Two cases were described. One case had a depressed fracture of the frontal bone—he was conscious but confused and irrational with loss of appreciation of time and place. He was shocked and so was given three pints of plasma and a fracture-dislocation of the ankle manipulated. Following this the respiration rate increased. The scalp wound was then redressed and he was given two pints of blood. On the following day the head injury was dealt with and the bony fragments removed. The patient became restless and the pulse again increased in rate and he died on the third day. Histological investigation in both cases revealed irregular hyperæmia of the brain with ring hæmorrhages associated with capillary fat emboli. Fat emboli were also demonstrated in the degeneration of the choroid epithelium.

DR. POLLAK described the clinical history and necropsy findings in a patient injured by an underwater explosion. No fractures were present in this case.

7. Observations on the Effects of Concentrated Plasma in Reducing Intragranial Pressure. (W. McKissock.)

W. MCKISSOCK had tried the use of 100 c.cs. of plasma which had been concentrated four times, but was unable to demonstrate any lowering of the C.S.F. pressure estimated by lumbar manometer readings nor any evidence that it possesses a therapeutic effect.

Some surprise was expressed by members at these results. Harvey Jackson had observed lowering of pressure in the brains of tumour bearers when concentrated plasma was given.

8. Subdural Hæmatoma following Ventriculography. (D. W. C. Northfield and J. Schorstein.)

Cases were reported by D. W. C. NORTHFIELD and J. SCHORSTEIN on subdural hæmatoma following ventricular puncture: an example in the posterior fossa after head injury was described by F. K. KESSEL. Full description will appear later.

9. Radiography of Foreign Bodies. (H. Jackson.)

H. JACKSON: He had seen a few examples in which foreign bodies retained in the hair have given rise to difficulty when interpreting radiographs—for this reason he advocated shaving the head before taking radiographs in the " blitzed " cases, since metal, masonry, wood, and glass, if it contains lead, obscures the picture. He thought it was important to obtain very good films, otherwise some foreign bodies which had penetrated the dura would be missed. He himself had removed a large piece of glass and others had found wood; large foreign bodies were sometimes left embedded in brain because they were translucent to X-rays. Stones and pebbles might be very difficult to see except in extremely good X-rays. He described experiences which illustrated the fallacy of negative X-ray reports made from poor films.

10. Traumatic Anosmia. (A. D. Leigh.)

A. D. LEIGH: Out of a study of 679 patients suffering from head injury, there were 44 cases of defects of smell; 28 showed a complete anosmia, and 16 were incomplete. In all these cases the post-traumatic amnesia and period of unconsciousness were long, and hospitalization a matter of months instead of weeks. Anosmia is a bad prognostic sign as regards fitness for Army service; 2 died, 16 were discharged from the Army, and 7 were placed in Category C. In only 3 cases had there been any evidence of recovery of smell.

C. P. SYMONDS stated that he had seen a case of slight head injury which had developed anosmia.

G. JEFFERSON expressed the view that it was important to separate the cases in which there was a shearing off of the olfactory nerve filaments from those of bruising of the olfactory tract. The former never recovered. It was best seen clearly in olfactory groove meningiomas. The problem was important from a medico-legal point of view.

11. The Intradural Approach for the Cure of Cerebro-Spinal Rhinorrhœa. (K. Eden.)

K. EDEN: With the accumulation of large numbers of cases, the question of cerebro-spinal rhinorrhœa becomes important. Lawson stated that this condition was always fatal in the course of time. Cairns recently pointed out that these cases may heal spontaneously. The danger of meningitis is not the only one, aerocele may arise and it may be necessary to operate. The mortality rate of those operated on had formerly been 30 per cent. It was thought that sulphonamide might diminish the danger and gave courage to operate on persistent cerebro-spinal rhinorrhœa. The disadvantage of the usual extradural approach was that there was a considerable risk of lighting up infection from the bone edges when the dura was separated from the edges of the opening into the nasal sinuses. He described two cases in which the leakage of C.S.F. had been stopped by an intradural operation through a small frontal bone flap. One had an aerocele. Both recovered. Sometimes it is difficult to localize the leak preoperatively, the intradural method gives good exposure.

D. W. C. NORTHFIELD stated that he had seen three cases of cerebro-spinal rhinorrhœa. Two ceased spontaneously after two weeks. The third case was a young woman who was concussed and remained unconscious for three weeks and then recovered. She had cerebro-spinal rhinorrhœa and she was observed for four weeks. She then had two attacks which might have been meningitis. After the second attack she was operated on and made a satisfactory recovery.

C. P. SYMONDS pointed out that the case for operative repair appeared to be satisfactory, but several questions arose. If there was a fracture in the posterior wall of the frontal sinus, should it be repaired as a routine? How common was this type of injury? He wished to know the proportion of cases which had a fracture of the skull over the sinuses; he thought that their number might be considerable, but had only had one complicated case of his own of late meningitis resulting from frontal fracture.

DR. GREENFIELD had only five cases in 20 years.

DR. SYMONDS stated that he would like to know what was the long-term prognosis of the cases operated on. Could we be sure that operation would certainly prevent meningitis appearing at a later date. If it was thought advisable to operate on all cases, then there was going to be a great deal of work to do. What was the risk of stirring up trouble by doing a severe operation immediately after injury.

H. CAIRNS said that in any figures one must take into account the deaths caused by the onset of meningitis immediately after injury. He had operated on one case in the early stages; this went well, but it was always a big undertaking. Theoretically, operations should be safe, but fully 50 per cent. of the cases had already infected frontal scalp wounds by the time they come to hospital. At the moment, with present X-ray methods, it is impossible to be certain what is the state of the posterior plate of the frontal air sinus. If one had reason to think that there was a wide defect in the posterior wall, then a fascia-lata graft should be applied. There was a sequel to one case which had been operated on some years ago. The patient had received an injury one year previously, associated with meningitis and aerocele. In this case the frontal sinus was explored. The patient returned one year later with a fatal attack of meningitis.

W. McKISSOCK asked whether it would not be possible for the society to collect the cases of cerebro-spinal rhinorrhœa and find out what was their subsequent history.

N. DOTT expressed the view that it must be very rare for cerebro-spinal rhinorrhœa to be associated with aerocele, because the brain becomes adherent to the margins of the fistula.

C. P. SYMONDS thought that the air in the frontal sinus would be aseptic so that the incidence of infection should be low. The question was raised of how long can one wait for the fistula to heal up? If there is severe bleeding from the nose, perhaps one should operate immediately. It might be preferable to use the extradural approach if the opening is far forward, but the intradural if the fracture extends further back.

HARVEY JACKSON pointed out that the patients who had severe nasal hæmorrhage often got cerebro-spinal rhinorrhœa. Fractures through the cribriform plate should be operated on early because the opening had a tendency to increase in size; 50 per cent. of the injuries to the frontal sinus closed by themselves, but the remaining cases did not do so. When the posterior wall was involved he thought that the mucosa lining the sinus should be removed.

12. Sulphonamide as a Local Prophylactic in Neuro-Surgical Operations. (G. Jefferson and H. Varley.)

G. JEFFERSON described some studies made with H. Varley on the sulphonamide content of aspiration fluid, blood, and urine after dusting 5·0 gm. into fresh wounds as a prophylactic measure. There had been only one postoperative wound infection in 9 months since the method had been applied. The figures will be published later.

13. Brain Abscess—Experimental. (Dorothy Russell, M. A. Falconer, and A. M. McFarlan.)

DOROTHY RUSSELL, M. A. FALCONER, AND A. M. McFARLAN: It has long been known that if an abscess is to be dealt with satisfactorily then it must have a capsule. When assessing the factors governing capsule formation, clinical studies alone do not give the required information. The technique in the rabbit is to open the skull and reflect the dura over a part of the left cerebrum. Ten days are allowed to elapse for the wound to heal and granulation tissue to form over the decompressed area. The brain inoculation is made through this area, using 0·2 c.c. of a mixture of agar and a broth culture of living organisms. The agar allows the organisms to proliferate. The reaction excited by agar alone is confined to the microglia which becomes activated to form foam-cells and occasional multinucleated giant cells. The advantages of the method are first, that if the brain swells the decompression serves to relieve the pressure; secondly, the granulation tissue over the site of inoculation minimizes the risk of diffuse meningitis.

In the investigations so far conducted it has been found possible to obtain circumscribed abscesses up to three months. If the inoculation has taken the decompression bulges, the bulge may subside and thereafter the animal remains healthy. Out of 36 experiments with a strain of hæmolytic streptococcus there was no infection in 6, localized abscess in 13, and abscess with spreading infection in 14. Growth in size of abscess depends upon centrifugal spread; spread is arrested in the region of increased vascularity by microglial infiltration. It would be a mistake to conclude that the time interval is constant for capsule formation and different types or organisms.

14. Bacteriological Studies of Abscess Contents. (A. M. McFarlan.)

DR. ALLAN M. McFARLAN said that he had examined pus from twenty-two cases of brain abscess and had isolated *Staphylococcus pyogenes* from six cases, *Streptococcus pyogenes* from two, a nonhæmolytic streptococcus from one, *Streptococcus pneumoniæ* from three, *Proteus vulgaris* from three, and mixtures of ærobes, or anærobes, or ærobes and anærobes from six. Previous workers had encountered a similar variety of organisms. It would be necessary to examine a large number of specimens before concluding which organisms were most commonly found, and

whether it was possible, as some authors asserted, to correlate the organism with the source of the infection, or with the formation of an abscess capsule, or with the clinical course of the abscess. He hoped that surgeons would continue to send him specimens from their cases so that he could study these points, and perhaps indicate how far it was legitimate to apply to human cases the results which Dr. Russell and Mr. Falconer were obtaining from their experiments on rabbits.

15. Brain Abscess. (J. B. Pennybacker.)

J. B. PENNYBACKER: 31 cases were seen in the Nuffield Department of Surgery, Oxford, in the last 3 years. There were 12 deaths, a mortality of 38 per cent. However, an analysis of the source of infection gave some grounds for optimism:

Classification as to source of infection:—

1. Metastatic: 11 cases. (A) Bronchogenic: 5 cases, 5 deaths. (B) From distant foci other than lungs: 6 cases, 1 death.
2. Mastoid Infections: 11 cases, 6 deaths. (A) Cerebral: 7 cases, 4 deaths. (B) Cerebellar: 4 cases, 2 deaths.
3. Frontal Sinus Infections: 4 cases, no deaths.
4. From Penetrating Wounds: 1 case, no deaths.
5. From Infections of Scalp and Skull: 4 cases, no deaths.

Thus the majority of deaths occurred in the cases due to primary lung sepsis and mastoid infections, and it was hoped that advances in chemotherapy would lessen the incidence of these diseases and their serious intracranial complications. Furthermore, if this series were adjusted to exclude the five bronchogenic abscesses, two undiagnosed (and untreated) ones, and three in which an aspiration was done when the patient was in extremis on admission, there were left 22 cases, in which deliberate treatment was undertaken and of these three died, a mortality of 13 per cent.

Most of the classical methods of treatment had been tried as follow: (1) Simple Drainage: 2 cases, 1 death. (2) Decortication and Open Drainage: 5 cases, 5 deaths. (3) Decompression and Aspiration: 3 cases, no deaths. (4) Decompression without Aspiration: 1 case, 1 death. (5) Untreated: 3 cases, 3 deaths (2 undiagnosed). (6) Extirpations: 17 cases, 2 deaths. (Primary Extirpation: 7 cases, 2 deaths. Extirpation after Aspirations: 10 cases, no deaths.)

The majority of cases were treated by eventual extirpation of the abscess. This means that they had to be kept alive until the abscess wall had attained a sufficient thickness to make it possible to dissect it out in toto. From observations in a few cases in which it was possible to assess the age of the abscess accurately, it seemed that a period of eight to twelve weeks from the onset of the cerebral infection was usually necessary. During this period, the risks are death (or visual failure) from increased intracranial pressure, and a widespread infection of the nervous system (usually from rupture of the abscess into the ventricular system or into the subarachnoid space). To prevent these complications, preliminary aspirations of the abscess were usually necessary, and a decompression might be required as well.

Aspiration was best done at the place where the abscess most nearly reached the convexity of the brain. In some cases (of metastatic abscesses, for instance) a ventriculogram might be necessary to show the position of the abscess, but many cases of abscess following frontal sinus and mastoid infections were eloquent enough to make ventriculography unnecessary.

Whether or not a formal decompression were done depends on the relief obtained by aspiration. The decompression in the first instance was usually an osteoplastic flap designed so that it could be used eventually for extirpation of the abscess. The dura was left unopened, but if this did not afford a sufficient decompression (as judged from the general condition of the patient), it might be necessary to open the dura over the abscess and protect the cortex with a sheet of gutta-percha tissue. This prevented adhesions to the bone flap and simplifies subsequent re-elevation of the flap.

Thorotrast was instilled into a number of abscesses, on the recommendation of Kahn, of Ann Arbor. Two cubic centimetres were instilled at the time of the initial aspiration; skiagrams then showed the site and size of the abscess, and afforded useful information for subsequent tapping and excision. In addition, there was some evidence to suggest that thorotrast evokes a microglial reaction in the wall of the abscess and might encourage the formation of a thicker capsule.

The technique of excision presented no peculiar problems. He had found it helpful to aspirate the abscess at an early stage of the dissection, even though it was usually impossible to do so without contaminating the field. On general grounds, a gross escape of pus is best avoided, but in many cases no harm came from the spilling of small amounts. The wounds were closed without drainage.

D. W. C. NORTHFIELD: During the past 5½ years he had treated brain abscess by drainage with tube or packing; out of 29 cases 15 died. He thought that with more mature judgment these figures were improving.

Analysis of Method of Treatment :—

	CASES	DEATHS
Drained	9	8
Aspiration and drain	1	0
Decompression without opening dura	1	0
Decompression with aspiration	5	3
Aspiration	6	3
Decompression with aspiration and enucleation	6	1
Enucleation	1	0

The danger of enucleation was the spilling of pus. Success could be obtained even with abscesses containing virulent organisms. He was convinced that nothing could be done about the cases in which infection was not localized. Chemo-therapy had been used in 14 cases, 7 of which died. The causes of death were as follows:—

	CASES
Multiple abscesses	4
Meningitis	4
Gross œdema	3
Pressure cones	2
Pulmonary embolus	1

Œdema may occur. In the massive type the œdema may involve the whole of one hemisphere and nothing that one could do appeared to have any effect. Pressure coning with involvement of vital centres caused death. The best method of dealing with the situation was by raising a flap, but without opening the dura.

The method of operating in favourable cases is as follows: A bone flap is elevated, the field is isolated by lintine wrung out in proflavine sulphate. The abscess is then needled; he washes the abscess cavity out with Proflavine or Milton at half strength. This dissolves stringy puss and he continues to do this until the fluid becomes clear. He leaves a little fluid in the cavity. Some cases have become sterile. Finally he inserts a little thorotrast which aids in the subsequent localization. He has been able to detect diminution in the size of the abscess. It is a mistake to leave the abscess too long, the waiting time had varied from six weeks to six months. If operation is performed at six weeks, then the capsule may rupture. If it is left too long, then fibrous trabeculæ form making excision difficult. He thought that two to three months was the best time for excision. In certain cases it might be necessary to aspirate the abscess through a burr-hole without elevating a flap, e.g. if the patient is too ill to be moved and is in another hospital.

C. P. SYMONDS mentioned that he had recently been surprised by the results of chemo-therapy and aspiration in two cases of brain abscess. He was doubtful if anything was to be gained by the enucleation of the abscess capsule.

G. JEFFERSON stated that he was somewhat puzzled because he felt that these results did not fit in with his experience, but the results were most creditable and had been presented and analysed in a very convincing way. They have demonstrated that cerebral abscess can sometimes be controlled by certain procedures. It would seem that in the end it does not matter whether the abscess is removed or drained. We do not know whether the scar of a healed abscess is worse than the scar of excision as a cause of epilepsy. The discussion gave one the impression that simple drainage was bad, but this does not fit with experience. Of 9 cases in 12 months all the single abscesses, 7 in number, had recovered. He demonstrated slides showing abscesses outlined with thorotrast; one temporal lobe abscess was of a

size so great that it seemed that whatever the result of drainage, to turn down a flap and excise would be a formidable procedure. This abscess was drained and disappeared. It is not necessary to drain an abscess from below, but from the most dependent point when the patient is lying in bed. Another case was a child who fell in the playground, a pebble was found in a wound, she came into hospital three weeks later desperately ill. Thorotrast was injected into the abscess and later drained and the child did very well. A third case was a boy with seven abscesses in the left temporal lobe—similar to a carbuncle; drainage would have been useless, so a temporal lobectomy was performed. This child had a stormy convalescence, developed a residual abscess which was drained, and the case recovered satisfactorily. A fourth case, an occipital cerebral abscess, developed 24 years after the original head injury, a shell wound. It was treated by tapping and was later excised. When doing this a small abscess at the tail was found which had not been demonstrated by thorotrast. It would seem that the important thing is to get the problem of infection over, when one reaches the stage when the abscess acts as a tumour then one can treat it satisfactorily. There were times when tapping succeeded, other times drainage, again excision might be best. Eventually we should be able to lay down rules for the employment of each of the methods.

N. DOTT stated that a displacement of the ventricles did not necessarily mean the presence of a cerebral abscess, because the resulting œdema from thrombophlebitis might give the same picture. He thought that intravenous sucrose might be helpful in nursing a cerebral abscess from the acute into the chronic phase, giving 70 c.cs. of sucrose daily; every day gained is useful. He had used this in a case in which bone has been removed over a considerable area. He thought that sucrose was able to break some vicious circle and improvement was maintained. He had found drainage to be valuable when pressure is a problem. He had left a catheter in an abscess, having pushed it along the course of the needle and had then slowly withdrawn the catheter 2 mm. a day; it may be necessary to do nothing further. Thorotrast had demonstrated the abscess shrinking to a small knob. Multiple abscesses might not be so bad as former speakers had indicated because he had successfully treated a case with four; three of these were drained and the fourth excised after seven months. His routine was to deal with the cause, get room for expansion either by raising a bone flap or bone removal, giving sucrose, and if the patient was losing ground he tapped the abscess, put a catheter in, and if it did not heal went on to excision.

H. CAIRNS thought that it was important to investigate the pus obtained from acute abscesses, we might find that it affected the prognosis, not in an individual, but as a general rule in a large series.

MR. J. E. A. O'CONNELL agreed with the undoubted benefit of tapping an abscess. He recalled a case of puerperal sepsis developing a cerebral abscess. An osteoplastic flap was turned down, but the dura was not opened. The abscess was tapped and 50 c.cs. of pus were removed. After a further two weeks the abscess was tapped again, the fluid was clearer. With successive tappings, the contents became clearer and eventually sterile. This was an advantage because excision could then be undertaken without risk of infection. He thought that abscesses following penetrating wounds should be drained because in these cases there is already some cerebral dysfunction.

D. W. C. NORTHFIELD agreed that the two cases described by Dr. Symonds were very impressive and showed the benefit of aspiration. He agreed with J. O'Connell that it was an important point that aspiration allowed the contents of an abscess to become sterile. He did not agree that a large abscess need deter enucleation; if it was of large size, it was difficult to drain. It should be tapped repeatedly until it had shrunk, then it could be removed. He thought that the period of hospitalization was less following excision than with drainage.

16. The Correlation of Sensory Tests with Histological Findings after Experimentally Produced Nerve Lesions in the Rabbit. (L. Guttmann, E. Gutmann, and G. Weddell.)

L. GUTTMANN, E. GUTMANN, AND G. WEDDELL: Sensory tests at a variety of different intervals were carried out following experimental section of the saphenous minor (sural nerve) or its adjacent nerves, the peroneal and tibial. It was possible to recognize with this method the autonomous, intermediate and maximal zones of the individual nerves. The area of sensory loss, tattooed into the skin after each test, progressively diminished before regeneration from the proximal stump had taken place. This shrinkage therefore must be due to an overlapping action of the surrounding nerves. Histological preparations were made of the skin, of the whole area supplied by the saphenous minor nerve and of a little beyond this at various

intervals after the nerve had been resected. When several tests (at approximately two-weekly intervals) had been done, the plexus of the nerves supplying the skin was found to be well within the earlier markings. The neurohistological boundary line was invariably found to follow closely the markings of the test just previous to the removal of the skin. The origin of the nerve fibres which grow towards the area of the sensory loss was discussed.

17. Observations on the Spinal Injuries of this War. (A. S. Kerr.)

A. S. KERR: Immediate observation of the level of complete sensory loss is important because if it remains the same then there is permanent damage of the cord. He thought that then open reduction for interlocked facet was harmful and that the fracture should be left alone and care taken of the bladder and the skin. In injuries of the cervical spine he thought that skull traction should be used in all cases showing cord signs or not. The first three cases were treated using steel wires through burr-holes with a 29-lb. traction. The burr-holes should be placed only a little in front of the spine—not too far in front or behind. Traction should be continued for three to four weeks before the plaster is applied. If the patient was paraplegic then traction should continue for six weeks because after this the skin appears to tolerate plaster better.

Care of the bladder is very important, he was against suprapubic cystotomy and thought tidal drainage should be used in every case. Suprapubic cystotomy has been performed because it was very easy to carry out, but it was impossible to keep it water-tight over a long time. Infection always occurred if the bladder is empty, it contracts down and leads later to frequency. He thought that laminectomy was justifiable under the following circumstances:

1. Presence of metallic bodies.
2. Increasing cord damage.
3. Radiographic evidence of bony encroachment.
4. When spinal block was present.

R. BARNES: Among air-raid casualties there was a greater proportion of severe spinal injuries with displacement and cord drainage than is ordinary civil practice. Forcible flexion was the cause. He reduced all cervical dislocations by extension under Pentothal. Reduction was confirmed by X-ray before applying plaster, which extended up to the head and down to the pelvis and should be kept on for three months. He described in considerable detail all the spinal injuries in one of the special centres. He has had two fractures of the axis without cord involvement; it might be associated with a second lesion at 4C. The pedicles of the axis were fractured with displacement of the body, taking the atlas with it. The dislocation in the second patient was not serious. The mechanism of the fracture was, perhaps, a severe blow on the base of the occiput causing flexion with loss of the protective influences of the neck muscles.

18. Fractures of the Axis Vertebra. (G. Jefferson.)

G. JEFFERSON: He spoke of the particularity of this injury, a fact which nobody appeared to have observed. It was a definite recurrent entity in large series of cases. The fracture occurred through the pedicles or sometimes through the articular facet and lamina. He described briefly its mechanism as a torque phenomenon, produced by the dispersal of lines of forces that took place owing to the absence of a superior articular facet on the superior surface of the pedicular component of this peculiar bone. This paper will appear in full later.

19. Cervical Plexus Injuries as an Extension of Brachial Plexus Injuries. (A. S. Kerr.)

A. S. KERR: Three cases were described in which brachial plexus injury was accompanied by loss of sensation from the angle of the jaw to the axilla with paralysis of the diaphragm. Sweating was absent in some of the cases. He could find no

references in the literature to injuries of the plexus of this sort, but imagined that they must have been overlooked. He was trying to work out the causation.

In discussion no members had seen examples, but Kerr thought it must be common and have escaped observation.

20. Blood Fibrin as a Styptic. (A. Dickson Wright.)

A. DICKSON WRIGHT: The history of brain surgery is really the history of hæmostasis—the various procedures for effecting this, he reviewed. The disadvantage of muscle graft was that it was not always available owing to the position of the flap. Cushing used to operate at the same time that a breast operation was being performed in another theatre. A. D. Wright suggested that it would be better to use fibrin. Plasma was not so good as serum because it would not filter, so it had been his practice to whip plasma in order to get fibrin. A skin-graft knife could be used to take a wafer or it could be rolled out into a sheet or pressed between glass. He gave an impressive demonstration of its utility.

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Dilantin Sodium Poisoning.—A case of dilantin sodium poisoning has been reported. In addition to pyrexia and severe widespread dermatitis that eventuated in dermatitis exfoliativa, marked enlargement of the liver and spleen developed. A recrudescence occurred five days after an apparent recovery. (R. M. S.)

Corpus Callosum: II. Higher Visual Functions following Complete Section.—In six epileptic patients in whom the corpus callosum was completely sectioned the higher visual functions in each homonymous field were studied. No disturbance of absolute or relative orientation, absolute or relative discrimination of size or recognition of colour, objects or letters was found in either homonymous field of vision. (R. M. S.)

Dulness as an Epileptic Equivalent.—A group of cases of "epilepsy" is reported in which periods of dulness, mental retardation, apathy and mild confusion occurred, lasting hours to days, in addition to definite attacks of typical grand mal, petit mal or psychomotor type. (R. M. S.)

Pick's Disease.—It is claimed by the authors that the outstanding and unique feature in Pick's disease is the discrepancy between the relatively mild parenchymatous changes and the severe neuroglial changes. (R. M. S.)

E.E.G. of Children.—A series of cases of so-called focal cortical seizures was studied by electroencephalographic, pneumoencephalographic, and clinical neurological methods. In none did electroencephalographic studies show that purely focal cortical disturbances were responsible for the seizures. (R. M. S.)

Retinal Artery Changes in Electric Shock Convulsions.—In cases of convulsions following electric shock a spasm of the retinal arteries usually precedes the generalized convulsion, and, as a rule, a spasm does not occur if the effect of the shock is to give only a minor seizure. In addition, if one can infer that the appearance of the retinal artery accurately reflects the condition of the smaller cerebral arteries, one may conclude that the arterial spasm does not cause the convulsion, but is itself an early part of the process sent into action by something else, in this case the electric shock. (R. M. S.)

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*The Pilocarpine Sweating Test: I. A Valid Indicator in Differentiation of Preganglionic and Postganglionic Sympathectomy. O. R. Hyndman, and J. Wolkin. 992.
*Sublingual Absorption of Prostigmine Bromide. H. M. Salzer. 1,007.

E.E.G. Classification of Epilepsies.—Different forms of electrical disturbance having been found with different forms of clinical seizures, the authors have used the electroencephalogram as a new basis for classification. The pattern of clinical seizure shows a close relationship to the form of the electroencephalogram, particularly with regard to localization. The localization of specific groups of neurons the excessive discharge of which marks the onset of an epileptic seizure and existing relations between these primary foci and the rest of the brain may determine both the form of the electroencephalogram and the pattern of clinical seizure, independent of the nature of the etiological factor in each case. (R. M. S.)

Involutional Melancholia.—It is the opinion of the authors that involutional melancholia is an exaggerated form of the climacteric syndrome and that treatment

with estrogenic substances is of value. Ten to twenty thousand units of estrone should be administered every other day until the patient shows improvement. (R. M. S.)

Human Pyramidal Tract.—There is great variability in the size of the large motor, or so-called Betz, cells in area 4 of man. Of the cells measuring between 900 and 4,100 square microns there is a somewhat gradual and uniform decrease in numbers from the smallest to the largest. In each third of the motor region there is a mixture of cells of various sizes, but all have a preponderance of the diminutive type. The upper third has more cells of all sizes than the middle portion, and the latter has more cells of all magnitudes than the lower third. The average size of the cells measured in the upper third is 1,978 square microns, in the middle third 1,702 square microns, and in the lower third 1,592 square microns. The term Betz or giant cell is non-specific. Therefore, it cannot be said with assurance that these cells give sole origin to the pyramidal tract fibres. (R. M. S.)

Peripheral Blood Flow in Schizophrenia.—The rate of peripheral blood flow in various mental states was studied by means of the venous occlusion plethysmograph method. The authors' studies demonstrate that there is no lesion of the arterial tree at the periphery in schizophrenia or in the other mental diseases studied. The conflicting results obtained in studies on circulation time in patients with schizophrenia can be attributed, in part at least, to the variable blood flow in the hand observed in this state. (R. M. S.)

Encephalopathy due to Burns.—An unusual case of encephalopathy attributed to burns is presented. Aphasia athetosis and mental deterioration ensued after the scald which affected 30 per cent. of the body surface. Pneumoencephalographic examination revealed dilatation of the third and lateral ventricles, and also cortical atrophy affecting the frontal and parietal regions. This damage to the nervous system is evidently assumed to have occurred within a period of fifteen weeks. (R. M. S.)

Intracranial Chordoma.—A case of intracranial chordoma arising from the clivus Blumenbachii with anterior extension into the retro-orbital space, causing unilateral proptosis, is reported. The histological features of the chordoma partially reduplicate the morphological features of the chorda dorsalis during its stages of evolution. Malignant infiltrating chordomas at the base of the brain have a tendency to include large blood vessels, thereby making surgical removal difficult. On the other hand, small, encapsulated, noninvasive chordomas might be eradicated by excision. (R. M. S.)

Pilocarpine Sweating Test.—After preganglionic sympathectomy pilocarpine hydrochloride ($\frac{1}{5}$ grain given hypodermically) will induce free sweating up to at least two years after operation. After postganglionic sympathectomy the pilocarpine test performed two months or longer after operation will demonstrate an anhidrosis, the area of which agrees precisely with that of the thermoregulatory anhidrosis. When two months at least has elapsed after operation, the sweat gland the postganglionic neuron of which has been severed will not respond to pilocarpine hydrochloride in $\frac{1}{5}$-grain doses. (R. M. S.)

Sublingual Absorption of Prostigmine Bromide.—As a result of the improved reaction to prostigmine bromide when given by the sublingual method, it has been possible to reduce the daily dose. Undoubtedly more rapid absorption takes place when the tablet is dissolved in the mouth. When parenteral administration of prostigmine methylsulphate is not available and a more prompt response from the drug is desired, sublingual administration of prostigmine bromide is recommended. (R. M. S.)

Porencephalic Cyst.—A case of porencephaly is presented with encephalographic and arteriographic studies demonstrating marked involvement of the middle cerebral artery in relation to the cerebral cyst. (R. M. S.)

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*Multiple Degenerative Softening: Clinicopathologic Report of Three Cases. G. B. Hassin and T. T. Stone. 1.
*Dietetic and Related Studies on Multiple Sclerosis. R. M. Brickner, N. Q. Brill, with the Assistance of F. M. Naylor and K. Montgomery. 16.
Lindau-Von Hippel Disease: A Report of Four Cases. W. McK. Craig, H. P. Wagener, and J. W. Kernohan. 36.
*Incidence and Cause of Death in Shock Therapy. J. L. Kinsey. 55.
*Multiple Primary Tumors of the Spinal Cord. B. W. Lichtenstein. 59.
*Cerebrospinal Fluid Dynamics in Man. E. Roseman, M. Rosenbaum, C. D. Aring, and E. B. Ferris. 72.
*Prevention of Traumatic Complications in Convulsive Shock Therapy by Magnesium Sulfate. H. E. Yaskin. 81.
*Prognostic Value of Intravenous Administration of Sodium Amytal in Cases of Schizophrenia. J. S. Gottlieb and J. M. Hope. 86.
*Histogenesis of Senile Plaques. T. L. L. Soniat. 101.
*Occlusion of the Superior Cerebellar Artery: Report of a Case with Necropsy. W. Freeman and D. Jaffe. 115.

Case Reports.

Marcus Gunn Phenomenon. F. D. Ingraham and J. B. Campbell. 127.

Multiple Degenerative Softening.—Three cases of disseminated degenerative softening were studied clinically and pathologically. The clinical features were indefinite and

varied in each case, but the pathological features were definite and similar in all. The essential pathological features were a combination of demyelination and inflammatory changes. The demyelination was in the nature of degenerative softening, caused by the direct action of a toxin on the nerve tissue, and was not of vascular origin. The pathological features of multiple degenerative softening can be produced experimentally by injecting into animals foreign substances such as extracts of brain tissue. (R. M. S.)

Dietetic Studies on Multiple Sclerosis.—An investigation was made on the life-long dietary habits of thirty-four patients with multiple sclerosis. In general, patients with multiple sclerosis are poor eaters, the consumption of visible fat, particularly of dairy fat, being especially poor. In seventeen patients (group 1) these defects were quite obvious. In five others (group 2) the material gave ground for strong suspicion that the defects existed. In eight (group 3) there was suggestive, but uncertain evidence, and in four (group 4) there were no signs of abnormality. Study of the relationship of food intake, weight, intercurrent events, and course of the disease suggested a possible connection between nutritional adequacy and the disease. (R. M. S.)

Death in Shock Therapy.—In shock therapy, the death rate is low—seventy-three per ten thousand patients treated with insulin and twenty-three per ten thousand patients treated with metrazol. (R. M. S.)

Multiple Primary Tumours of Spinal Cord.—The clinical and pathological features of two cases of multiple intra-medullary tumours of the spinal cord are presented. Multiple intra-medullary tumours are most frequently ependymomas, and they may be associated with Recklinghausen's disease of the central nervous system. The association of ependymomas with neurinomas and meningiomas is emphasized. The clinical course of such tumours may be greatly protracted and frequently many of the growths are asymptomatic. (R. M. S.)

C.S.F. Dynamics in Man.—The authors describe a new type of neck cuff which appears to compress effectively the deep veins of the neck. The response of the cerebrospinal fluid pressure to jugular compression, either in terms of magnitude or of rate of rise, may be greatly influenced by (1) the manner in which the neck veins are compressed; (2) the initial cerebrospinal fluid pressure; (3) leakage of cerebrospinal fluid; (4) hyperventilation; (5) variations in intracranial blood flow, and (6) pathological block in the spinal subarachnoid space. A knowledge of these variable factors should aid in the clinical interpretation of dynamic responses of the cerebrospinal fluid pressure. (R. M. S.)

Prevention of Traumatic Complications in Shock Therapy.—Solution of magnesium sulphate, a drug with a curare-like action, has proved to be satisfactory for prevention of traumatic complications in convulsive shock therapy. The dosage of magnesium sulphate is more accurate and easier to gauge with relation to the patient than that of curare, as the margin of safety is much greater. The preparation of this drug is relatively simple and economical. (R. M. S.)

Administration of Sodium Amytal in Cases of Schizophrenia.—The type of response obtained by the intravenous injection of sodium amytal is of distinct aid in the evaluation of the prognosis for a given schizophrenic patient. The more closely the patient's behaviour approaches normal under the influence of the drug, the better the prognosis. The reactions produced by the drug may be helpful in the evaluation of new types of therapy. (R. M. S.)

Histogenesis in Senile Plaques.—The great majority, if not all, of senile plaques arise primarily from nerve cells which have undergone degeneration: in a great proportion of these cells the degeneration consists of Alzheimer's neurofibrillary change. The resulting necrobiotic focus (consisting of remnants of nerve cells, axons, dendrites, and neurofibrils) attracts the microglia cells, which, while attempting to function in their physiological role, may become a part of the plaque. The oligodendroglia cells most probably become involved in the plaque by mere coincidence. There is evidence that the astrocytes, at least at times, attempt glial repair of the plaque. Methods of research are, as yet, not adequate enough to provide an explanation of the complex biochemical processes which cause degeneration of the nerve cells, and hence initiate formation of the senile plaque. (R. M. S.)

Occlusion of Superior Cerebellar Artery.—A case of occlusion of the superior cerebellar artery is presented, with correlation of the clinical picture and the post-mortem observations. The classic aspects of the syndrome of the superior cerebellar artery are reviewed, and some atypical features are discussed with a view to correlating the anatomic lesions and indicating some problems of functional localization. (R. M. S.)

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Analysis of One Hundred Cases of Schizophrenia with Recovery. T. A. C. Rennie, with the Assistance of J. B. Fowler and A. B. Baltimore. 197.

*Fiber Connections of Corpus Striatum as Seen in Marchi Preparations. S. W. Ranson, S. W. Ranson, Jr., and M. Ranson. 230.

*Acute Postoperative Aseptic Leptomeningitis: Review of Cases and Discussion of Pathogenesis. A. I. Finlayson and W. Penfield. 250.
*Pathologic and Mental Alterations in a Case of Simmonds' Disease. R. C. Wadsworth and C. McKeon. 277.
*Displacement and Herniation of the Hippocampal Gyrus through the Incisura Tentorii: A Clinico-pathologic Study. G. A. Schwarz and A. A. Rosner. 297.
*Influence of Locomotion of the Plantar Reflex in Normal and in Physically and Mentally Inferior Persons: Theoretic and Practical Implications. P. I. Yakovlev and M. J. Farrell. 322.
*Patterns of Cerebral Integration Indicated by the Scotomas of Migraine. K. S. Lashley. 331.

Case Reports.

Anosognosia and Autotopagnosia. C. W. Olsen and C. Ruby. 340.

Fibre Connections of Corpus Striatum.—In this investigation isolated lesions were made in various parts of the corpus striatum with the Horsley-Clarke apparatus, and the resulting degenerations analysed through the study of Marchi preparations. The results obtained correct certain misapprehensions and clarify some ambiguities regarding the myelinated efferent fibres of the globus pallidus. This is an important research which does not lend itself to a brief abstraction. (R. M. S.)

Acute Postoperative Aseptic Leptomeningitis.—According to the authors, acute postoperative aseptic leptomeningitis has the following mechanism. There persists, after operation, a cavity at the site of operation, particularly when removal of a neoplasm or scar has been extensive. This fills with blood clot, and the clot subsequently undergoes liquefaction and degeneration. Its products, high in protein, accumulate and are periodically discharged into the general subarachnoid space, either indirectly, through a ventricle which has been opened by the operative procedure, or directly, through subarachnoid channels from the cisterna magna. (R. M. S.)

Pathological and Mental Alterations in Simmonds' Disease.—A case of Simmonds' disease is presented which appeared after child-birth and was associated early in the course of the illness with a manic depressive psychosis. The pituitary gland showed a unique, progressive, nonspecific granulomatous process resembling allergic necrosis. There was secondary atrophy of the thyroid, adrenals, parathyroids, ovaries, uterus, and breasts. These atrophic processes were accompanied by the development of marked cachexia and microsplanchnia. Scattered focal lesions observed in the central nervous system are attributed not to the psychosis but to the repeated attacks of hypoglycæmia. Degenerative lesions in the supraoptic and paraventricular nuclei of the hypothalamus are thought to be secondary to destruction of the anterior lobe of the pituitary gland. (R. M. S.)

Displacement of the Hippocampal Gyrus.—Medical displacement and herniation of the hippocampal gyri into the space of Bichat and through the incisura tentorii occurred in 83 per cent. of a hundred cases of a supratentorial expanding lesion. Such herniations were present in most cases of increased intracranial pressure from any cause. Then they were rather narrow, slight, and usually equal on the two sides. Midline and parasagittal lesions produced equal, marked herniations with little lateral difference. Unilateral cerebral lesions, in the temporoparietal region notably and in the temporal lobe particularly, produced a significant group of changes in the basilar region. These were: ipsilateral medial displacement and herniation of the hippocampal gyrus; contralateral shift of the brain stem, hypothalamus and optic chiasm and tracts with distortion of these structures, and, less frequently, hæmorrhages in the brain stem and hippocampal, fusiform, and occipital gyri. (R. M. S.)

Influence of Locomotion on Plantar Reflex.—The extensor response of the big toe can, in certain persons, be induced by physical exertion. The authors claim that the occurrence of a Babinski sign following exertion has a characteristic relation to the type of exertion and to such factors as a history of prenatal and early postnatal developmental abnormalities, influencing the ultimate constitutional organization of the individual. (R. M. S.)

Cerebral Integration in Migraine.—Maps of the scotomas of ophthalmic migraine sketched at brief intervals during an attack suggest that a wave of intense excitation is propagated at a rate of about 3 mm. per minute across the visual cortex. This wave is followed by complete inhibition of activity, with recovery progressing at the same rate. Sometimes the inhibition spreads without the preceding excitatory wave. Limitation of the disturbance to the primary visual cortex raises questions as to the nature of the interconnections between architectonic fields. The observations are interpreted in relation to the possible integrative effects of radiating waves of excitation in the cortex. (R. M. S.)

BRAIN

Vol. 64. No. 1. March 1941.

*The Phenomenon of Myotonia. D. Denny-Brown and S. Nevin. 1.
*Vitamins E and B_6 in the Treatment of Muscular Dystrophy and Motor Neurone Disease. G. Fitzgerald and B. McArdle. 19.
*Visual Object-Agnosia with Special Reference to the Gestalt Theory. W. Russell Brain. 43.
*The Significance of Lesions in the Dentate Nuclei apparently Consecutive to Disease of the Frontal Lobes. G. E. Smyth. 63.
*Unilateral Exophthalmos (Proptosis): Causation and Differential Diagnosis. G. Joly Dixon. 73.

Myotonia.—Electro-myographic records show that the mechanism of delay in relaxation of voluntary muscular contractions in both myotonia atrophica and congenita is due to a complex abnormality. The difficulty in relaxation is partly due to myotonia recurring in the muscle itself, but is mainly caused by a reflex spasm of the prime movers and synergists, of central origin. This double abnormality affects the pharmacological approach to the disease. The peripheral abnormality is hyperexcitability of the muscle fibre, which leads to repetitive discharge, probably merely an exaggeration of the normal state. The prolonged reflex discharge may lead to hypertrophy in muscles which were not otherwise myotonic. This is especially seen in Thomsen's Disease and acquired myotonia. (D. J. W.)

Vitamins E and B_6 and Motor Neurone Disease.—Ten cases of muscular dystrophy and ten cases of motor neurone disease were adequately treated with Vitamins E or B_6 alone or in combination without clinical or biochemical evidence of improvement. The authors draw attention to the validity of the experimental basis for the positive claims made by other observers. (D. J. W.)

Visual Object-Agnosia.—A boy of seven developed visual object-agnosia with alexia, agraphia, finger and lateralizing agnosia, and constructional apraxia. The boy's case is reported in detail, and the effect of these defects upon his intellectual development and appreciation of forms is described. There did not appear to be any evidence of a disorder of visual Gestalt-formation, but the interpretation of visual agnosia in terms of the Gestalt theory is discussed. (D. J. W.)

Lesions in Dentate Nuclei consecutive to Disease of Frontal Lobes.—Pathological cell changes were found in the contralateral dentate nuclei of four Subjects of unilateral frontal lesions, although the cerebellar, cortex, and pontine nuclei were normal. These changes support the anatomical evidence that most of the superior cerebellar peduncle fibres connect with the cortical areas 4 and 6, through cell stations in the thalamus. They also support the view that cerebellar function is exerted through the cortex and not through the extrapyramidal motor system. The observations also explain the simulation of cerebellar disfunction occurring with frontal lesions and make their incomplete nature, their variability and tendency to regress, more easily understood. (D. J. W.)

Unilateral Exophthalmos.—Symmetrical proptosis of the eye may be due to a mass within the cone of extraocular muscles, or, usually glioma or meningioma; lymphatic and venous engorgement, or paresis of the muscles. In the last two cases, the proptosis is reducible. Asymmetrical proptosis indicates a mass outside the cone of muscles. The symptoms of speed of onset, papill-œdema, usual and papillary changes, often pain, are indicated. (D. J. W.)

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*Experimental Cerebral Concussion. D. D. Brown and W. R. Russell. 93.
*Spinal Cord Degeneration produced by Dietary Means. D. Mitchell. 165.
*Familial Cortical Cerebellar Atrophy. B. Hall, K. B. Noad, and O. Latham.

Experimental Cerebral Concussion.—Experimental concussion in cats, dogs, and monkeys who have been lightly anæsthetized with nembutal, causes temporary abolition of brain stem and spinal reflexes. A steep rise of blood pressure can usually be demonstrated. This effect is also observed in the decerebrate preparation. Experimental concussion was readily produced with a specially designed pendulum which struck the animal's head with a velocity of 25–30 feet per second, the head being free to move a few centimetres. An identical injury with the head fixed caused no concussion. This "acceleration concussion" corresponds in mechanism to the common head injury as it occurs accidentally. With this type of injury death was often caused without any histological lesion of the brain, and there was no significant change in intra-cranial pressure. Compression of the brain also causes respiratory and reflex failure, but the mechanism is different from that observed in acceleration concussion, as also is the effect of arterial occlusion sufficient to cause anæmia of the brain. The paralysis of concussion is immediate and is associated with an increased blood flow through the brain: there is no evidence of vascular spasm in the brain. The paralytic phenomena observed in acceleration concussion are due to a direct physical injury to the neurones. The effect of petechial hæmorrhages in the medulla and cervical cord was observed to develop one to four minutes after the injury. Contusions of the cerebral hemisphere caused by blows on the basal dura had no effect on the bulbar mechanisms unless resulting cerebral hæmorrhage caused a great increase of intra-cranial pressure. Increasing severity of injury causes a more prolonged paralysis of concussion. The reaction of the cerebral cortex is probably similar to that observed for the pons and medullary centres. (W. R. R.)

Spinal Cord Degeneration produced by Diet.—Young pigs were fed on an inadequate diet, and demyelization occurred in the posterior columns of the cord. The

amount of ataxia seen in these animals was related to the amount of yeast in the diet; but as autoclaving did not affect the results, the deficiency was thought to be inorganic and not that of a vitamin. Two pigs, deprived of vitamin A, but receiving adequate amounts of yeast, showed no ataxia. One showed peripheral myelin loss in the spinal cord, while the others, to whose diet vitamin A was restored, did not. (D. J. W.)

Familial Cortical Cerebellar Atrophy.—An heredo-familial ataxia of cerebellar type similar to that described by Holmes in 1907, was encountered in two generations of a family. One autopsy revealed a pure chronic cortical parenchymatous atrophy involving the Purkinje cells with secondary degeneration of the olivary neurones. (D. J. W.)

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An Early Human Embryo, with 0·55 mm. Long Embryonic Shield. T. B. Johnston. 1.
A Macroscopic Study of the Nerve Supply of the Stomach. G. A. G. Mitchell. 50.
The Normal Occurrence, Structure and Homology of Prostate Glands in Adult Female *Mastomys Erythroleucus Temm.* F. W. Rogers Brambell and D. H. S. Davis. 64.
Some Observations on the Cardio-Vascular System in the Viable Fœtal Lamb. K. J. Franklin, A. E. Barclay and M. M. L. Prichard. 75.
Further Observations on the Structure of Human Heart-Valves. W. F. Harper. 88.
The Evolutionary Significance of the Embryology of the Amphibian Nephric System. R. J. O'Connor. 95.
Note on the Independence of Sesamoid and Epiphysial Centres of Ossification. R. Wheeler Haines. 101.
A Study of the Subcortical Connexions of the Optic Tract System of the Ferret, with Special Reference to Gonadal Activation by Retinal Stimulation. J. M. Jefferson. 106.
Anatomical Notes: The Amount of Mucosal Tissue in the Small Intestine. C. P. Martin and J. Banks. 135.
The Application of Trichrome Staining Methods in Embryological Technique. J. S. Baxter. 137.

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*Cell Columns in the Spinal Cord of a Human Fœtus of Fourteen Weeks. G. J. Romanes. 145.
The Chorion and Endometrium of the Embryo H.R.1. T. B. Johnston. 153.
The Cutaneous Ligaments of the Digits. J. Grayson. 164.
The Mechanical Anatomy of the Carpus and its Bearings on Some Surgical Problems. M. A. MacConaill. 166.
*The Angioarchitecture of the Thalamus in the Rabbit. B. Schlesinger. 176.
*The Normal Histology of the Thalamus in the Phalanger, *Trichosurus Vulpecula*. F. Goldby. 197.
*Observations on the Association Fibre System of the Visual Cortex and the Central Representation of the Retina. W. E. Le Gros Clark. 225.
The Dental Comb of Lemurs. D. Roberts. 236.
*The Differentiation of the Brain and other Tissues in an Implanted Portion of an Embryonic Head. P. Glees. 239.
Tension Lines, Cleavage Lines and Hair Tracts in Man. F. W. Jones. 248.
The Distribution of Ascorbic Acid (Vitamin C) in the Early Stages of the Developing Chick Embryo. S. A. Barnett and G. Bourne. 251.
ANATOMICAL NOTES: A Stereoscopic X-Ray Method of Reconstruction. W. R. M. Morton. 265.
Note on the Histology of Lymph Nodes in *Echidna*. M. A. Basir. 267.

Cell Columns in Spinal Cord of Human Foetus.—The cell columns in the cervical and lumbar enlargements of a human fœtus are described and compared, and several points of similarity are shown. The cell columns are already adult in their arrangement by the fourteenth week of fœtal life. (G. W.)

Angioarchitecture of Thalamus in Rabbit.—A description of the angioarchitecture of the thalamus has been given. There are no individual nuclear arteries in the thalamus, for the areas vascularized by the parenchymal arterioles do not coincide with those of the nuclei or their subdivisions. Individual nuclei have a composite vascularization and any one parenchymal arteriole supplies parts of adjacent nuclei and fibre tracts. The lack of correspondence between individual nuclei and individual vascular territories is a very common feature in the brain, and the existence of arterial areas involving adjacent fragments of grey and white matter provides no foundation for the theory of functional constancy which claims that functional units existing in the brain have arteries of their own throughout evolution, and that they may even be homologized on the basis of their arterial supply throughout a phylogenetic series. (G. W.)

Normal Histology of Thalamus in Phalanger.—The thalamus of Trichosurus Vulpecula has been described on the basis of serial sections of normal brains stained by toluidine blue, a modification of the Weigert method, and by Davenport's silver method. In structure it is essentially similar to the thalamus of Didelphys virginiana (Bodian, 1939, 1940) and to that of primitive placental mammals; it shows, however, a number of progressive features in which it resembles rather closely the published account of Tupaia (Clark, 1929a). These progressive features are shown most clearly in the following observations. The lateral geniculate body (dorsal nucleus) is laminated as in higher mammals. The nucleus lateralis posterior (the equivalent of the pulvinar) is large, and differentiated into medial and lateral parts. A possible

representative for the " pars arcuata " has appeared in the ventral complex. There is a well-marked lateral differentiation in the dorsomedial nucleus which appears to correspond with the main part of that nucleus in the higher primates. Commissural fibres between two sides are feebly developed. In nearly all other respects the structure is that typical of primitive mammals in general and no undoubted marsupial specializations were observed. (G. W.)

Association Fibre System of Visual Cortex.—In three experimental lesions in the visual cortex of the monkey, the examination of Marchi material failed to show the existence of long association fibres leading to other parts of the visual cortex, or to the cortex in front of the lunate sulcus. These negative results are in accordance with the results of recent electro-physiological studies of the cortex. In one of the experiments there was an indication of association fibres leading from the visual cortex to a narrow strip of peristriate cortex lying under cover of the occipital operculum. The organization of the visual cortex in relation to the projection of retinal impulses is discussed. (G. W.)

Differentiation of Brain in Implanted Portion of Embryonic Head.—An account is given of the differentiation of tissues in a portion of the head of a 12-days embryo, implanted in the brain of a young rabbit. The differentiation of nervous tissue had proceeded to the formation of a definite cortical structure with a laminar arrangement of ganglion cells, of groups of cells showing a nuclear arrangement, and of circumscribed fibre tracts. (G. W.)

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A Human Ovum at the Previllous Stage. J. H. Dible and C. M. West. 269.
Epiphysial Structure in Lizards and Marsupials. R. W. Haines. 282.
*The Termination of Optic Fibres in the Lateral Geniculate Body of the Monkey. P. Glees and W. E. Le Gros Clark. 295.
*An Experimental Investigation of the Visual System in the Phalanger, *Trichosurus vulpecula*. A. D. Packer. 309.
*The Sensory Component of the Hypoglossal Nerve in the Rabbit. J. D. Boyd. 330.
*The Pattern of Cutaneous Innervation in Relation to Cutaneous Sensibility. G. Weddell. 346.
*The Effect of Denervation on the Structure and Hormonal Responses of the Monkey Prostate. G. I. M. Swyer and S. Zuckerman. 368.
ANATOMICAL NOTE: A Note on the Actions of the Cruciate Ligaments of the Knee Joint. R. Wheeler Haines. 373.

Optic Fibres in Lateral Geniculate Body of Monkey.—Seven days after section of one optic nerve in the monkey, the corresponding laminæ in the lateral geniculate body are filled with thickened terminal fibres and enlarged and deeply staining boutons. These laminæ, therefore, stand out in strong contrast with the normal laminæ which receive the terminal fibres of the intact optic nerve. It is established that each main optic nerve fibre commonly terminates in a spray of 5–6 branches, and therefore in relation to 5–6 geniculate cells. The boutons of the degenerate optic fibres lie in contact with the cell body, and no geniculate cell is related to more than one bouton. By the study of the degenerating terminal fibres and boutons direct evidence has been provided in confirmation of the conclusion, previously based on transneuronal atrophy that crossed optic fibres end in laminæ 1, 4 and 6 of the lateral geniculate body, while uncrossed fibres end in laminæ 2, 3, and 5. (G. W.)

Visual System in Phalanger.—The normal anatomy and histology of the optic chiasma, optic tracts, lateral geniculate body, superior colliculus and area striata of the cerebral cortex have been studied by means of serial sections stained by the Weigert method (Weil's modification) and by toluidin blue. These structures have been shown to be essentially similar to those in other primitive mammals (marsupial or placental) except for the marked lamination of the lateral geniculate body. Their connections have been studied by the use of the Marchi, retrograde and transneuronal degeneration techniques, following enucleation of an eye, or the placing of lesions in the area striata. The experimental results are summarized as follows: (1) All fibres of the optic nerve are myelinated, all degenerate after section of the nerve, and about 75 per cent. of them cross in the optic chiasma. The 25 per cent. which remain uncrossed lie ventrolaterally in the chiasma, and superficially in the beginning of the optic tract; as the tract passes dorsally they become mixed with crossed fibres. (2) Crossed retinal fibres can be traced to the dorsal and ventral nuclei of the lateral geniculate body, to the superior colliculus and to the nucleus opticus tegmenti via the anterior accessory optic tract and the transverse peduncular tract. Uncrossed retinal fibres can be traced only to the lateral geniculate body (dorsal nucleus), but the possibility that a few go to the superior colliculus cannot be excluded. No evidence was found for retinal connections with the nucleus lateralis posterior of the thalamus or the pretectal nucleus; if such connections are present they must be scanty. (3) In the lateral geniculate body (dorsal nucleus) crossed and uncrossed fibres end chiefly in alternate laminæ; the ventral quarter of this nucleus is poorly laminated and receives only crossed fibres. (4) Corticopetal fibres

from the lateral geniculate body end mainly (probably exclusively) in the area striata, where there is a reversed representation of the parts of the lateral geniculate body similar to that described in the opossum (Bodian, 1935) and other mammals. Corticofugal fibres from the area striata can be traced to the lateral geniculate body (dorsal nucleus) and to the superior colliculus of the mid-brain, but to no other parts of the nervous system. (G. W.)

Sensory Component of Hypoglossal Nerve in Rabbit.—At no stage in the development of the rabbit hypoglossal nerve could a dorsal root or ganglion of the Froriep's type be found. Muscle spindles, or other specialized sensory endings could not be found in the intrinsic muscles of the rabbit's tongue. In the extrinsic muscles, although muscle spindles are absent a few atypical endings can be found close to the attachment of the muscles to the mandible and hyoid bone. The macroscopic and microscopic anatomy of the rabbit hypoglossal nerve, when considered in relation to the relevant experimental findings, appears to demonstrate that any afferent fibres in the nerve can reach the central nervous system only by way of the upper cervical dorsal roots. (G. W.)

Relation of Cutaneous Innervation to Cutaneous Sensibility.—The cutaneous nerve plexuses in skin from Acanthias vulgaris, the rabbit, the rhesus monkey, and Man are constructed on a similar pattern. Only one type of nerve ending was seen in skin from Acanthias vulgaris, two types were seen in skin from the ear of the rabbit, and multiple types in skin from the monkey and from Man. The pattern of cutaneous innervation in skin from the ear of the rabbit has been demonstrated. It is such that in general each unit area is evenly innervated by fibres approaching it from all directions. A single nerve fibre in the dorsal nerve at the base of the ear of the rabbit breaks up into terminal ramifications which are distributed to approximately three hundred hair follicle groups. The terminal ramifications of a single nerve fibre distributed to hair follicles in the ear of the rabbit cover an approximately circular area of 1 cm. in greatest diameter. Each hair-follicle group and each hair is innervated by at least two separate nerve fibres whose terminal ramifications are evenly interlocked with each other. After section of approximately one-quarter of the dorsal ear nerve in the rabbit, degenerating nerve fibres can be seen throughout the whole extent of the skin of the dorsum of the ear. The size of a single superficial nerve net in skin from the pad of the thumb of the monkey covers an approximately circular area of 1·5 cm. in diameter. It is closely interlocked with nerve nets from neighbouring areas. Multiple groups of Krause's end-bulbs are found beneath each cold spot in the skin of the human forearm. They are situated about 1 mm. from the skin surface and are borne on widely separated nerve fibres. A single isolated superficial nerve net in a hypoalgesic area of skin from the dorsum of the hand in Man covers an approximately circular area of 0·75 cm. in greatest diameter. This distance corresponds to the limen of two-point discrimination for pain in a similar normal area. The pattern of sensory loss after certain nerve root, nerve plexus, and nerve trunk lesions in Man has been described. The pattern of sensory recovery after certain complete nerve trunk interruptions has been described. The clinical findings have been correlated with the histological findings and discussed. (G. W.)

Denervation and Hormonal Responses of Monkey Prostate.—Division of the sacral parasympathetic fibres alone or of the sacral and hypogastric nerves together appears to have no effect on the histological structure of the immature rhesus prostate; in this respect the monkey behaves like the dog, guinea-pig, and rabbit. On the other hand, division of the hypogastric nerves was without effect on the prostate of an almost mature monkey; a result which is not fully in accord with Golub's observations on dogs. Androgenic stimulation leads to rapid maturation of the prostate after division of the sacral nerves while division of the hypogastric nerves has no effect on the responses of the prostate to œstrogenic stimulation. (G. W.)

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A Presomite Human Embryo with a Neurenteric Canal (Embryo R.S.). P. N. B. Odgers. 381.
Contribution to the Study of the Morphogenesis of the Thyroid Gland. K. E. Sgalitzer. 389.
*Cytological Changes in Senility in the Trigeminal Ganglion Spinal Cord and Brain of the Mouse. W. Andrew. 406.
*The Laminar Organization and Cell Content of the Lateral Geniculate Body of the Monkey. W. E. Le Gros Clark. 419.
*The Termination of Optic Fibres in the Lateral Geniculate Body of the Cat. P. Glees. 434.
*The Multiple Innervation of Sensory Spots in the Skin. G. Weddell. 441.
*The Motor Cortex in *Galago* and *Perodicticus*. S. Zuckerman and J. F. Fulton. 447.
*The Nerve Supply of the Mammalian Ductus Arteriosus. J. D. Boyd. 457.

Cytological Changes in Senility in Trigeminal Ganglion, Spinal Cord, and Brain of Mouse.—The cells of the trigeminal (semi-lunar) ganglia and of the ventral horn of the spinal cord show definite qualitative differences between young and senile mice. There are certain changes in the nerve cells in old age common to all parts of the nervous system of the mouse studied thus far. Other changes in senility

are more or less specific for different regions: (a) The changes common to all regions are a decrease in Nissl material, increased basophylic properties of the nucleus, increasing paleness of the nucleolus, loss of regularity of cell outline, and degeneration and death of some of the cells. (b) The change most characteristic of the ventral horn cells is pigment accumulation, which is found in senile animals in almost 100 per cent. of the cells. (c) The change most characteristic of the trigeminal ganglion is vacuolar degeneration. (d) An increase of interstitial elements about degenerating cells has been found in all regions except the layer of Purkinje cells. These satellites consist, in the central nervous system, primarily of oligodendrogliar cells; and in the ganglia, of amphicytes. The role of such cells seems to be almost undoubtedly phagocytic. The astrocytes of the mouse brain do not show signs of degeneration in senility. (G. W.)

Laminar Organization and Cell Content of Lateral Geniculate Body in Monkey.—A wax reconstruction model of the lateral geniculate body of the monkey is described and figured. The crossed and uncrossed fibres of the optic tract do not become segregated until they have penetrated the lateral geniculate body. Computations of the cell content of the lateral geniculate body have been made by a direct method of counting, and also by estimating the number of cells involved in retrograde atrophy following a localized cortical lesion of known dimensions. The number of cells in the small-celled laminæ is assessed at approximately 1,590,000, and in large-celled laminæ 209,000. Approximately 1,350 fibres of the optic radiation project on to each square millimetre of the visual cortex. Evidence is adduced that, so far as the retinal fibres ending in the large-celled laminæ are concerned, approximately 60 per cent. are crossed and 40 per cent. uncrossed. All the cells of the large- and small-celled laminæ project on to the visual cortex, and no evidence is found for the existence of intercalated neurones in the nucleus. (G. W.)

Termination of Optic Fibres in Lateral Geniculate Body of Cat.—It has been found in the cat that the optic fibres arising as collaterals from the optic tract terminate in the lateral geniculate body in special end-formations, i.e. fine terminal rings. After section of an optic nerve these optic terminals undergo a characteristic degeneration. The number of synaptic contacts of optic terminals with one principal cell of the geniculate body is estimated to be about forty. Synaptic contacts are established with the dentrites as well as with the cell body. The axo-dendritic contacts are more numerous than the axo-somatic. The evidence suggests that one optic fibre covers with its terminal branches an area containing about ten cells. It is almost certain, however, that the same region receives a supply from more than one optic fibre and that there is an extensive overlap. (G. W.)

Multiple Innervation of Skin Sensory Spots.—Microscopical evidence has been brought forward which shows that in an area of acute tactile sensibility (finger pad) in the human skin each " spot " is commonly innervated by two or three nerve fibres approaching from different directions, and ending in separate Meissner's corpuscles. (G. W.)

Motor Cortex in Galago and Perodicticus.—The motor area in Galago is not bounded either rostrally or caudally by sulci. It extends below and above the sulcus rectus and on to the upper part of the medial surface, the hindlimb area being dorsal to the forelimb zone. In perodicticus the motor area lies rostral to the central sulcus and a line projected upwards and downwards from its dorsal and ventral extremities. The general disposition of representational parts of the body is the same as in man. Extirpation of the motor area in both species leads to motor defects which rapidly clear up, but which, over a period of three weeks, are still demonstrable. (G. W.)

Nerve Supply of Mammalian Ductus Arteriosus.—The mammalian ductus arteriosus possesses a sensory innervation very similar to that possessed by the aorta and the carotid sinus. This nerve supply is derived from the left vagus nerve and, when it is present, from the left aortic nerve. Fine nerve fibres, presumably motor, are also found terminating in relation to the muscular coat of the ductus, but the available material does not permit of a statement as to their origin. The distal portion of the pulmonary trunk and the proximal portions of the pulmonary arteries also possess a sparse afferent innervation. The nerve supply of the ductus arteriosus is discussed in relation to the behaviour of the ductus at birth. (G. W.)

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A Presomite Human Embryo (Shaw) with Primitive Streak and Chorda Canal, with Special Reference to the Development of the Vascular System. R. J. Gladstone and W. J. Hamilton. 9.
A Comparative Study of the Inferior Tibio-Fibular Joint. A. Carleton. 45.
The Capillary Bed of the Central Nervous System in a Member of a Second Genus of Gymnophiona —*Siphonops*. E. Horne Craigie. 56.
*The Early Stages in the Degeneration of Cutaneous Nerve Fibres. G. Weddell and P. Glees. 65.
Variations in Organ Size caused by Chronic Treat-

ment with Adrenal Cortical Compounds. An Example of a Dissociated Adaption to a Hormone. H. Selye. 94.

Observations on the Cardio-Vascular System and Lungs of an African Elephant Fœtus. E. C. Amoroso, K. J. Franklin, and M. M. L. Pritchard. 100.

*The Development and Significance of the Cell Columns in the Ventral Horn of the Cervical and Upper Thoracic Spinal Cord of the Rabbit. G. J. Romanes. 112.

*The Lateral Geniculate Body in the Platyrrhine Monkeys. W. E. Le Gros Clark. 131.

Degeneration of Cutaneous Nerve Fibres.—An account of the early stages in Wallerian degeneration which follow nerve section in the skin of the dorsum of the rabbit's ear has been given. The results of methylene-blue staining, silver impregnation, and specific staining for myelin have been compared. The Schwann cells in the skin from the dorsum of the rabbit's ear show no reactions to vital dyes for 336 hours after nerve section. In skin from the dorsum of the ear of normal unoperated rabbits a small proportion of the nerve fibres show evidence of either regenerative or degenerative changes. Similar changes have been seen in a piece of skin from the elbow region of a human subject. These changes are most marked in the cutaneous nerve plexus. There is an appendix which contains an atlas of 91 photographs showing the early stages in the degeneration of cutaneous nerve fibres. (G. W.)

Development of Cell Columns in Ventral Horn of Rabbit Spinal Cord.—The adult anatomy and development of the motor cell columns in the ventral horn of the cervical enlargement in the rabbit are described in relation to the developing peripheral structures. Four chief stages have been noted: (1) A thickening in the ventral part of the germinal epithelium of the neural tube to form a ventral horn. (2) The outgrowth of processes from the ventral horn cells, the latter grouping themselves together to form longitudinal aggregations. (3) The secondary splitting of these aggregations into subsidiary columns of cells coinciding with their connection to the muscles which they supply, but prior to reflex activity. (4) The appearance of co-ordinated neuro-muscular activity leading to contraction of the peripheral muscles. In this stage true Nissl granules appear in the cytoplasm of the ventral horn cells. The establishment of neuro-muscular connections, which are distinct only in the last stage, proceeds peripherally from segment to segment along the limb, a new column appearing as each segment is innervated. Thus the columns are embryologically related to segments of the limb, and there is evidence in the adult to suggest that such a functional relation exists, though it is not complete owing to the unsatisfactory nature of the chromatolytic reaction. (G. W.)

Lateral Geniculate Body in Platyrrhine Monkeys.—A description is given of the laminar organization of the lateral geniculate body in six genera of New World monkeys. The laminar organization is less highly differentiated in these monkeys than it is in the catarrhine primates. Within the group of New World monkeys the laminar organization is most highly differentiated in Cebus, and least in Ateles and Saimiri. The significance of the variability in laminar organization is discussed. (G. W.)

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Vol. 20. No. 3. May 1941.

Further Observations on Skin Reactions to Antigens from Heterologous Cestodes in Echinococcus Disease. J. T. Culbertson and H. M. Rose. 249.

Calcium and Phosphorus Metabolism in Osteomalacia. XI. The Pathogenic Rôle of Pregnancy and Relative Importance of Calcium and Vitamin D Supply. S. H. Liu, H. I. Chu, H. C. Hsu, H. C. Chao, and S. H. Cheu. 255.

Observations on the Effect of Streptococcal Upper Respiratory Infections on Rheumatic Children: A Three-Year Study. A. G. Kuttner and E. Krumwiede. 273.

An Epidemic of Influenza B occurring in a Group of Rheumatic Children Concurrent with an Outbreak of Streptococcal Pharyngitis: Clinical and Epidemiological Observations. G. Reyersbach, T. F. Lenert, and A. G. Kuttner. 289.

*Studies of Calcium and Phosphorus Metabolism. XVI. The Influence of the Pituitary Gland. W. Bauer and J. C. Aub. 295.

Acid-Base Balance, Renal Function, and Gastric Secretion during Hypochloremia in the Dog. J. B. Kirsner and K. Knowlton. 303.

Clinical Studies on Pyridoxine (Vitamin B_6). J. Flexner and M. R. Chassin. 313.

Demonstration that the Cell Plasma Ratio of Blood contained in Minute Vessels is Lower than that of Venous Blood. R. V. Ebert and E. A. Stead. 317.

The Clearance of Bilrubin from the Plasma. A Measure of the Excreting Power of the Liver. A. A. Weech, D. Vann, and R. A. Grillo. 323.

Pituitary Gland and Calcium and Phosphorus Metabolism.—Patients with acromegaly were shown to have an increased urinary excretion of calcium and phosphorus, but blood and fæcal values were normal. The degree of abnormality paralleled the severity of the disease, X-ray therapy caused less abnormality. (J. N. C.)

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*Measurement of the Sensitivity of the Smallest Blood Vessels in Human Skin: Responses to Graded Mechanical Stimulation in Normal Men. J. R. Di. Palma, S. R. M. Reynolds, and F. I. Foster. 333.

Blood Iodine in Patients with Thyroid Disease. D. S. Riggs, E. F. Gildea, E. B. Man, and J. P. Peters. 345.

Lung Volume under Surgical Anesthesia: The Effect

of Avertin on the Subtidal Air. G. E. Lindskog and A. D. Spicer. 355.
The Relation of High and Low Urea Clearances to the Unilin and Creatinine Clearances in Children with the Nephrotic Syndrome. K. Emerson, P. H. Futcher, and L. E. Farr. 361.
Spontaneous Recovery from Nutritional Macrocytic Anemia in Young Swine following Initial Estrus. S. G. Smith, R. Reiser, and G. T. Harrell. 369.
*Studies on the Chemical Diagnosis of Pellagra (Nicotinic Acid Deficiency). H. Field, D. Melnick, W. D. Robinson, and C. F. Wilkinson. 379.
Vitamin A and Carotene. I. The Determination of Vitamin A in the Blood and Liver as an Index of Vitamin A Nutrition of the Rat. P. B. Horton, E. Leiberman, and L. H. Newburgh. 395.
Metabolism, Toxicity and Manner of Action of Gold Compounds used in the Treatment of Arthritis. I. Human Plasma and Synovial Fluid Concentration and Urinary Excretion of Gold during and Following Treatment with Gold Sodium Thiomalate, Gold Sodium Thiosulfate, and Colloidal Gold Sulfide. R. H. Freyberg, W. D. Block, and S. Levey. 401.
The Liver Lipids and their Distribution in Disease. An Analysis of 60 Human Livers. E. P. Ralli, K. Paley, and S. H. Rubin. 413.
Studies in Blood Histamine in Patients with Allergy. II. Alterations in the Blood Histamine in Patients with Allergic Disease. B. Rose. 419.
Magnesium Partition Studies in Graves' Disease and in Clinical and Experimental Hypothyroidism. L. J. Soffer, C. Cohn, E. B. Frossman, M. Jacobs, and H. Sobotka. 429.
*Proceedings of the Thirty-Third Annual Meeting of the American Society for Clinical Investigation held in Atlantic City, N.J., May 5, 1941. 433.

Sensitivity of Blood Vessels in Skin.—A method is described for measuring the excitability of the smallest blood vessels in human skin. The effect of certain physiological variables is demonstrated. (J. N. C.)

Chemical Diagnosis of Pellagra.—Chemical studies show that no urinary abnormal "nicotinic acid" values are found in patients with pellagra. There is, however, a decrease in urinary trigonelline in deficient subjects. (J. N. C.)

Proceedings of Thirty-Third Annual Meeting.—P. 440: **Studies in Blood Flow.**—A method for recording changes in blood flow in the intestinal mucosa has been developed and changes seen in physiological conditions are described. P. 445: **Replacement of Potassium by Sodium in Muscles of Normal Dogs.**—It was shown that subcutaneous injections of desoxycorticosterone acetate caused muscular weakness with a loss of potassium and a replacement by sodium in the muscles. Administration of potassium chloride prevented this chemical change and also the paralysis. P. 446: **Peripheral Nature of Muscular Weakness of Familial Periodic Paralysis.**—G. D. Gammon and A. M. Harvey. (Title only.)

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Influences of Erythrocytes and of Leukocytes on Stability and Transfer of Ascorbic Acid in Human Blood. M. Heinemann. 467.
Evidence for General Distribution of Peripheral Resistance in Coarctation of the Aorta: Report of Three Cases. J. M. Steele. 473.
Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex. A. J. Patek and J. Post. 481.
The Intravenous Glucose Tolerance Test. E. L. Lozner, A. W. Winkler, F. H. L. Taylor, and J. P. Peters. 507.
The Peripheral Vascular Response to Exercise in the Hyperthyroid State. D. I. Abramson and S. M. Fierst. 517.
*Studies on Pain. Observations on Pain Due to Local Cooling and on Factors Involved in the "Cold Pressor" Effect. S. Wolf and J. D. Hardy. 521.
Formulæ for Afferent and Efferent Arteriolar Resistance in Normal Human Kidney. An Application to the Effects of Spinal Anesthesia. H. Lamport. 535.
The Relative Changes in Afferent and Efferent Arteriolar Resistance in the Normal Human Kidney. H. Lamport. 545.
Mechanisms of Respiratory Failure under Barbiturate Anesthesia (Evipal, Penthothal). H. K. Beecher and C. A. Moyer. 549.
Clinical Studies with the Aid of Radioactive Phosphorus. 1. The Absorption and Distribution of Radio-Phosphorus in the Blood and Its Excretion by Normal Individuals and Patients with Leukemia. L. A. Erf and J. H. Lawrence. 567.
Studies on Neoplasms with the Aid of Radioactive Phosphorus. III. The Phosphorus Metabolism of the Phospholipid, Acid Soluble and Nucleoprotein Fractions of Various Tissues of Normal and Leukemic Mice following the Administration of "Tracer" and "Therapeutic" Doses of Radio-Phosphorus. L. W. Tuttle, L. A. Erf, and J. H. Lawrence. 577.
Experimental and Clinical Studies on Gramicidin. W. E. Herrell and D. Heilman. 583.
Acute Hemolytic Anemia from the Sulfonamides. C. L. Fox and R. Ottenberg. 593.
Spectrophotometry of Fairley's New Blood Pigment, Methemalbumin. C. L. Fox. 603.

Studies in Pain.—Pain caused by local cooling is separate from the sensation of cold. It appears to be mediated by Class C fibres. The intensity of the pain depends on the degree of cooling. The stimulus required for the production of "cold pain" may be found in the thermal gradient in the tissues of the part immersed. It may be that this stimulus brings about a painful vasospasm in the part. The "cold pressor" effect is a measure of reaction to pain. (J. N. C.)

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The Incidence of Conjugal Neurosyphilis. E. L. Hutton. 313.
The Contribution of the Rorschach Method to Clinical Diagnosis. W. D. Ross. 331.
Fatigue and the Effort Syndrome. E. Guttmann and H. Rimoldi. 349.
Treatment of Emotional Problems in Childhood. W. H. Whiles. 359.
The Mental Sequelæ of Head Injury. H. A. Palmer. 370.
Psychogenic Episodes in the Course of Major Psychoses. E. W. Anderson. 383.

A Survey of Skin Testing, with Observations on a Suggested Method in Epileptics. D. C. Dewar. 397.
Convulsion Therapy in War Psychoneurotics. R. Good. 409.
A Self-governed Patients' Social Club in a Public Mental Hospital. J. Bierer and F. P. Haldane 419.
Observations in Hypoglycæmia. II. Blood Sugar and Consciousness. W. Mayer-Gross and F. Berliner. 427.
Arachnodactyly (Dolichostenomelie of Marfan). E. C. Dax. 434.

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Discussion on Ear, Nose and Throat Disease in Mental Disorder. Introduction by the President. T. C. Graves. 477.
Sinus Trouble and Personality. H. G. B. Russell. 479.
On the Curability of Mental Diseases by "Shock" Treatment. R. Freudenberg. 529.
A Study of Erythrœdema Polyneuritis (Pink Disease). T. A. Ratcliffe. 545.
On the Ætiology of the Fugue States. E. Stengel. 572.
Hyperostosis Frontalis Interna: Its Relationship to Cerebral Atrophy. R. M. Stewart. 600.
The Allergic Factor in Idiopathic Epilepsy. D. C. Dewar. 608.
Cutaneous Nævus with Buphthalmos and Epilepsy: Case Report. Redvers Ironside and D. Hill. 631.
Scheid's Cyanotic Syndrome. H. A. Palmer. 635.

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Vol. 93. No. 6. June 1941.

Bilateral Fracture of the Femoral Necks caused by Metrazol-Induced Convulsions. S. Androp. 701.
*The Post-Hospital Adaptation of a Selected Group of Patients with Dementia Præcox. J. L. Hoffman, E. H. Parsons, and M. W. Hagan. 705.
Esophagal Spasm. W. B. Faulkner. 713.
Colour Blindness and Tone Deafness Restored to Health during Psychotherapeutic Treatment using Dream Analysis. K. R. Stewart. 716.
Protrusion of Two Intervertebral Disks in the Cervical Region. T. T. Stone, A. J. Arieff, and C. Brown. 719.
Paramyoclonus Multiplex of Friedreich. E. S. Brewster. 723.
The Physico-Social Basis of Mental Disorder. G. W. Kisker and G. W. Knox. 731.
Allergy and Nervous Diseases. N. W. Winkelman and M. T. Moore. 736.
*Permeability Changes in the Brain induced by Metrazol and Insulin Convulsions. E. A. Spiegel and M. Spiegel-Adolf. 750.

Adaptation of Patients with Dementia Præcox.—A study of the progress of 127 patients with dementia præcox from the U.S. Army has particular value because of the early detection, adequate hospitalization, and facilities for rehabilitation on discharge. After a period varying from 1–12 years 28 per cent. were well adjusted, 25 per cent. tolerably adjusted with assistance, 35 per cent. were again in hospital, 2 per cent. were in goal, and 10 per cent. had died. (W. M. H.)

Permeability Changes in Brain Induced by Metrazol and Insulin.—Taking conductivity at high and low frequencies as the measure the authors find the polarizability of brains of guinea pigs to be lowered after convulsions induced by metrazol and insulin. They consider this a sign of increase in the permeability of cellular surface films. (W. M. H.)

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The Paralysing Effect of Fright. E. F. Reaser. 1.
Insulin Hypoglycemia and the Electrocardiogram. B. E. Goodrich and F. J. Smith. 10.
The Chronic Alcoholic as a Neurotic and a Dreamer. B. Karpman. 17.
The Innervation of the Limbs. J. A. Abbott and M. Moore. 41.
Hypnotic Suggestion: Its Dynamics, Indications, and Limitations in the Therapy of Neurosis. S. Lorand. 64.
Psychopathological Disorders in the Mother. M. Huschka. 76.

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Blood Phosphorus in Mental Diseases. F. Pascual del Roncal. 133.
The Etiology of the Psychosis of Dementia Paralytica. With a Preliminary Report of the Treatment of a Case of this Psychosis with Metrazol. V. B. Kenyon and D. Rapaport. 147.
*The Effect of Menstruation on Seizure Incidence. Willard W. Dickerson. 160.
The Post Concussion Syndrome. J. M. Wittenbrook. 170.
Compact Container for Olfactory Tests. M. T. Moore. 177.
Music—An Aid in Management of Psychotic Patients. I. M. Altshuler and B. H. Shebesta 179.
A Case of Infantilism in a Male, cured with Hormones. S. Koster. 184.

Menstruation and Seizure Incidence.—Of a series of 269 patients 10 per cent. showed a relation between menstruation and epileptic fits, 12 per cent. had no fits during their menses, and the remaining 78 per cent. showed no relation. (W. M. H.)

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*Estrogen Therapy in the Psychoses. C. C. Burlingame and M. B. Patterson. 265.
Preliminary Survey of Motility in Children. J. D. Teicher. 277.

Experimental Insulin Shock, particularly in the Guinea Pig. F. M. Allen. 305.
Asymptomatic Vertebral Fractures in Epilepsy. M. T. Moore, N. W. Winkelman, and L. Solis-Cohen. 309.
The Deforming Dystony: Its Kinesiologic Analysis. M. S. Burman. 324.
A Syndrome of Time-Agnosia. G. M. Davidson. 336.

Estrogen Therapy and Psychoses.—Estrogenic substances (estradiol benzoate and estrone) favourably influence menopausal depressions. Thus 59 per cent. of 63 cases of involutional psychoses and 52 per cent. of 27 manic depressive psychoses in the depressed stage showed definite improvement. The improvement rate in mixed psychoses and schizophrenia was found to be unaltered by like therapy. (W. M. H.)

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Vol. 4. No. 3. May 1941.

Multiple Motor Innervation of the Frog's Sartorius Muscle. B. Katz and S. W. Kuffler. 209.
Fast Central Fibers in Fish. Properties of Mauthner and Müller Fibers of Medullospinal System. H. T. Graham and J. L. O'Leary. 224.
*Availability of Lactic Acid for Brain Oxidations. J. Wortis, K. M. Bowman, W. Goldfarb, J. F. Fazekas, and H. E. Himwich. 243.
*Cortical Extinction in Convulsions. R. Meyers. 250.
*Influence of Frequency of Stimulus upon Response to Hypothalamic Stimulation. K. Hare and W. A. Geohegan. 266.
*Experimental Study of Gastric Activity released from Cortical Control. F. H. Hesser, O. R. Langworthy, and L. C. Kolb. 274.

Innervation of Sartorius Muscle.—In the frog's sartorius muscle a maximal nerve stimulus produces a large synchronous spike of short latency at both the pelvic and fibial regions. This is accounted for by multiple nerve endings on most fibres. If some myoneural junctions are put out of action by cutting one of the main nerve branches, by partial curarization, or by combined application at suitable intervals of stimuli to the motor nerve and nerve-free pelvic end of the muscle, a part of the normal synchronous early potential is abolished and replaced by a wave of long latency. From study of the latency and shape of the spike two or three discrete narrow " neural " zones with the majority of the myoneural junctions may be mapped. (W. M. H.)

Lactic Acid for Brain Oxidations.—That oxidation of lactic acid alone will not support cerebral function is shown by the failure of injected lactate to rouse patients in hypoglycæmic coma or to prevent hypoglycæmic convulsions in hepatectomized dogs. (W. M. H.)

Cortical Extinction in Convulsions.—Cortical potentials and excitability following electrically induced convulsions were studied in ten human subjects with paroxysmal convulsive disorders. Cortical extinction following a convulsion is shown by lack of response to supraliminal cortical stimuli; during the period of extinction the cortical electrogram is isoelectric. For a brief period thereafter the cortex near the epileptogenous focus may show increased excitability, a liminal stimulus evoking a seizure of greater violence. (W. M. H.)

Hypothalamic Stimulation Response.—In cats the hypothalamus was stimulated with electrodes manipulated stereotactically. The magnitude of pressor and respiratory responses was found to increase with the frequency of stimulation up to several hundred per second beyond which figure the response diminished. In some instances changes of frequency altered the character of the response. For this reason strict localization of areas for pressor, depressor, pupillary dilator, and constrictor responses is questionable. (W. M. H.)

Gastric Activity and Cortical Control.—The smooth muscle of the stomach and œsophagus is shown to be similar to vesical muscle in its central nervous control. In cats cerebral ablations alter stomach activity, contractions being stronger and more persistent, tone in distension increased and a marked stretch reflex with delayed relaxation of the stomach wall appearing on sudden distension.

(W. M. H.)

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*The " Motor " Cortex of the Chimpanzee. J. G. Dusser de Barenne, H. W. Garol, and W. S. McCulloch. 287.
*Functional Interdependence of Sensory Cortex and Thalamus. J. G. Dusser de Barenne and W. S. McCulloch. 304.
*Suppression of Motor Response obtained from Area 4 by Stimulation of Area 4S. J. G. Dusser de Barenne and W. S. McCulloch. 311.
*Functional Organization of Sensory and Adjacent Cortex. J. G. Dusser de Barenne, H. W. Garol, and W. S. McCulloch. 324.

" Motor " Cortex of Chimpanzee.—In young chimpanzees under dial the effects of electrical stimulation were studied in the entire sensory cortex. As in the macaque responses depend on the parameters of stimulation. All parts of the sensory cortex yield contraction of skeletal muscles save two bands III and VII which, with two others just outwith, cause suppression of motor responses to cortical stimulation, suppression of motor after discharge after cortical stimulation, and relaxation of skeletal muscles. In the parietal area facilitation and existing

muscular tension are necessary for motor responses. Otherwise the results of electrical stimulation agree with those of strychninization. (W. M. H.)

Interdependence of Cortex and Thalamus.—Corresponding cortical areas and sensory thalamic nuclii are shown to be functionally interdependent, impairment of one or of the mutual pathway causing a decrease in the spontaneous electrical activity of the other. (W. M. H.)

Motor Response Suppression by Stimulation.—Suppression of motor responses to electrical stimulation of area 4 by electrical or other stimulation of area 4S does not depend on corticocortical connections, the nucleus caudatus, putamen, globus, pallidus, thalamus, substantia nigra, or cerebellum. Its long latency indicates an indirect "delay" path; its long duration suggests a continuous activity antagonistic to the activity excited by stimulation of area 4 rather than an extinction of that activity. The failure of suppression to affect the knee jerk is, however, not easily explicable on this hypothesis. Suppression may also be obtained from areas 8S, 2S, and 19S from which suppression of electrical activity of the cortex can be obtained although its occurrence is not dependent upon the suppression of cortical activity. (W. M. H.)

Functional Organization of Cortex.—The effects of strychninization on activity of adjacent cortical areas is schematically summarized for the monkey. Subdivision of areas 5 and 7 into bands as in the chimpanzee has not been shown. (W. M. H.)

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Volume of Interfibre Spaces in Frog Muscle and the Calculation of Concentrations in the Fibre Water. P. J. Boyle, E. J. Conway, F. Kane, and H. L. O'Reilly. 401.
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Effect of Light on Red Blood Cells. The Light Sensitivity of Blood from Different Vertebrate Species. W. Meyerstein. 510.

Acetylcholine in C.N.S.—In the spinal cord of the dog ACh occurs in the grey matter and in the efferent white matter, but not in the afferent. In the brain of the cat the distribution of ACh does not run parallel to that of cell bodies or synapses. The cerebral cortex is relatively rich, while nuclei and tracts vary considerably. (W. M. H.)

Skeletal Changes in Vitamin A Deficiency.—In the absence of Vitamin A the bones of the growing dog show an increase in osteoblastic and osteoclastic activity with resulting proliferation of cancellous at the expense of compact bone. The positions of bone overgrowth in the skull and vetrebral column described account for degenerative changes in the brain, cranial and peripheral nerves, the posterior root ganglia and anterior root nerves. The greatest hypertrophy is in the bones of the posterior fossa and of the cervical column. Advanced cases of Vitamin A deficiency show an increase in C.S.F. pressure and internal hydrocephalus. (W. M. H.)

Ether and Absorption Rate of Saline.—Ether in small concentration reduces the rate of absorption of normal saline solution from the subarachnoid space in animals anæsthetized with avertin, amytal, or chloralose. It is concluded that ether causes a dilatation of cerebral vessels. (W. M. H.)

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Differentiation of an (Amphibian) Water Balance Principle from the Antidiuretic Principle of the Posterior Pituitary Gland. H. Heller. 125.
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Further Evidence Concerning the Role of the Hypothalamus in the Induction of Ovulation in the Rabbit following Injections of Copper Acetate. G. W. Harris. 231.

Histamine and Reactive Hyperemia.—A new technique of assaying small amounts of histamine with guinea pigs' ileum is described. In reactive hyperæmia in man

and in the rabbit the histamine content of venous blood is unaltered. Cysteine prevents the fall of blood pressure on injection of histamine in the cat, but fails to modify the fall in reactive hyperæmia. (W. M. H.)

Afferent Discharges from Sense Organs.—The importance and size of representation in the receiving area of the cortex for different parts of the body surface varies in different animals; thus in the rabbit the mouth parts, in the cat the claws, in the monkey the hand and face are more important. The afferent volley produced by touch shows a potential wave in the cortex with its first phase surface positive due to activity in the afferent fibres. It may be followed by a rhythmic after discharge from the thalamus. The consecutive efferent waves seen in chloralose anæsthesia are mainly surface negative and associated with discharge of impulses from the cortical neurones. Convulsant drugs increase the efferent responses. Under dial or nembutal afferent discharges may have little effect on cortical activity; and in deep anæsthesia with chloroform and ether afferent discharges may fail to reach the cortex. In light ether touch may produce widespread activity in other parts of the cortex. Auditory and visual stimulation may produce general increase in activity. Signals from tactile receptors are shown to be passed to the cortex without much alteration, frequencies varying as in afferent nerves. (W. M. H.)

Gaseous Tensions in Brain.—CO_2 tension of air from the human ventricle 3 hours after ventriculography was found to be slightly higher than that of the jugular blood and much higher than that of the arterial blood. Oxygen was found to diffuse out from the enclosed air. In cats a like change in gaseous tensions occurred more quickly. (W. M. H.)

Oxygen Lack and Cerebral Circulation.—Oxygen lack is found not to increase the arterio-venous (torcular sinus) oxygen difference in cats until the inspired air contains less than 15 per cent. oxygen. Presuming cerebral metabolism is unaltered it is concluded that only severe degrees of anoxæmia increase the cerebral circulation. Increase is due to rise in blood pressure and partly to a dilatation of the cerebral vessels caused by a rise in lactic acid. Other factors preventing fall in oxygen tension in brain tissue are the increase in pulmonary ventilation and the change in the oxygen dissociation curve in anoxæmia. (W. M. H.)

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*Potassium Accumulation in Muscle and Associated Changes. P. J. Boyle and E. J. Conway. 1.
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*On the Permeability Change of Stimulated Nerve. J. F. Danielli. 117.

Potassium Accumulation in Muscle.—Under suitable conditions potassium will gather against a gradient in excised sartorius muscle without increase in weight. The quantitative relations of its entrance are accurately described by theoretical equations based on considerations of osmotic, electrical, and Donnan equilebria. The principle seen in the change of diffusible anion to indiffusible with corresponding entry of potassium to the cell may be of general application to cells. (W. M. H.)

Morphothebaine Dimethylether.—Morphothebaine-dimethylether, an alkaloid closely related to bulbocapnine and corydine, in general resembles ergotoxine in its effects but differs in having no primary stimulant action on smooth muscle in paralysing more readily the peripheral cardio accelerator mechanism of the heart, in causing "adrenaline reversal" on the blood pressure and uterus of the rabbit and not in the cat, and in having a very transient action in the intact animal. (W. M. H.)

Permeability Change of Stimulated Nerve.—If the lipoid part of the plasma membrane of nerve oxons be a binolecular film composed of two partly expanded monolayers, then the injury potential might arise from an increase in the degree of expansion and the increase in the permeability, on discharging the injury potential, from a reversion to close packed film with gaps permeable to ions. The heat evolved by condensation into micelles and by flow of ions across the membrane is calculated and in its limits shown to agree with the value for initial heat found in experimental conditions. The theory presented would explain the increase in accommodation with K and Ca. (W. M. H.)

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BOOK REVIEWS

THE NURSING COUPLE

M. P. Middlemore

(Hamish Hamilton, London. 1941. Pp. 195. 7*s.* 6*d.*)

This essentially popular book views breast-feeding from the psychological standpoint. A timely attack is made on the artificial régimes often imposed on " nursing couples " and a plea is made for a more understanding consideration of each case. Unfortunately the study is based on a small number of cases. No detailed reports are given from which to assess the validity of the elaborate behaviouristic classification. The biological support for certain interpretations may be questioned. However, though patchy, the book is quite readable, and may encourage in the mother a sane approach to nursing.

DISEASES OF THE NERVOUS SYSTEM. DESCRIBED FOR PRACTITIONERS AND STUDENTS

F. M. R. Walshe

(Second Edition. E. and S. Livingstone, Edinburgh. 1941. Pp. 325. 12*s.* 6*d.*)

Evidence of the author's success in producing a lucid and simple text-book meeting the needs of student and practitioner comes in the early exhaustion of the first edition. The appreciation and use of this admirable work must considerably further the study and practice of medicine to-day. When publishers are experiencing difficulty in getting supplies it is heartening to know that a large second edition with improvements and extended text has been possible. Among the improvements are new plates and an expansion of the sections on organization and symptoms of the sensory, visual, and speech functions, head and spinal injuries, and acute infections of the nervous system.

The chapter on space occupying lesions of the cranium in its amended form gives a simple description of the mechanisms which bring about a rise in intracranial pressure and rightly emphasizes the fact that the relative role of each varies in different cases. Many readers, however, might rightly carp at a simplification which assigns local symptoms of brain tumour to (1) tissue anoxia, and (2) tissue destruction. However appealing a suggestion it may be, that the main cause of disorder of function is impaired blood supply has yet to be proven, and it seems to us this reservation might well be pointed out in the text.

From the recasting the section on the pituitary emerges in none too laudable a form. The short account of the physiology of the gland ignores points which are essential to the practitioner and student for an understanding of the disorders of the pituitary described. The range of its hormonal influence is inadequately indicated. For example, its part in sugar metabolism, water and chloride balance and thyroid activity is not mentioned. Repeated recourse to the ugly word hypopituitarism does nothing to help crystallize ideas on the various types of altered function seen clinically. In a book which presents such a high standard of lucidity and adequacy shortcomings of this sort deserve comment. So too mention must be made of the failure to indicate the use of chloride in the treatment of bromide intoxication. The student should be explicitly told that treatment for the bulk of cases consists of common salt orally with fluids.

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